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NOVEL AND EFFECTIVE METHODS FOR α-THIOALKYLATION OF AROMATIC COMPOUNDS

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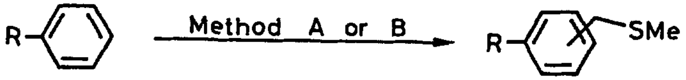
Summary: *Convenient and effective methods for the introduction of a methylthiomethyl group and other α-thioalkyl group into aromatic compounds are described.*

Friedel-Crafts type alkylation is a fundamental and important methodology for the creation of a new C-C bond to aromatic systems. Concerning the methylthiomethylation, however, direct reaction of CH_3SCH_2Cl with benzene in the presence of Lewis acid gave benzyl methyl sulfide only in poor yield (35%).1) Furthermore, a few reliable methods2,3) are also available for the α-thioalkylation[4] of unactivated benzene derivatives. In view of its high synthetic potential of a methylthiomethyl group and other α-thioalkyl groups connected to aromatic systems, it is strongly desired to explore a more convenient and effective procedure.

For this purpose we have examined the electrophilic reactivities of commercially available reagents, methyl methylsulfinylmethyl sulfide (FAMSO, **1**)5) or methylthiomethyl p-tolyl sulfone (MT-sulfone, **2**),6) which were developed as the nucleophilic reagents with the aid of bases. We envisaged that these reagents are also able to work as electrophilic synthons in the light of the novel ability of sulfone or sulfoxide as a good leaving group in the presence of Lewis acids.[7] These predictions are now born in fact.

Our methylthiomethylation (MTM) of aromatic skeleton is carried out in the two ways. These are **(A)** MTM-FAMSO method, in which aromatic substrate is added at an appropriate temperature (see Table I) to a solution of excess FAMSO/$AlCl_3$ in CH_2Cl_2 and **(B)** MTM-MTS method, in which MT-sulfone (**2**) is used instead of FAMSO.[8] The results of these experiments are summarized in the Table I. Most of the reactions were complete within 1 hr and yields were very good with benzene and simple alkylbenzenes and fairly good or moderate with halobenzenes, hetero-substituted benzenes and 5-membered heterocycles. These results show clearly the effectiveness of the present method when compared with the related reactions via Pummerer rearrangement.3)

Table I. Methylthiomethylation of Aromatic Compounds



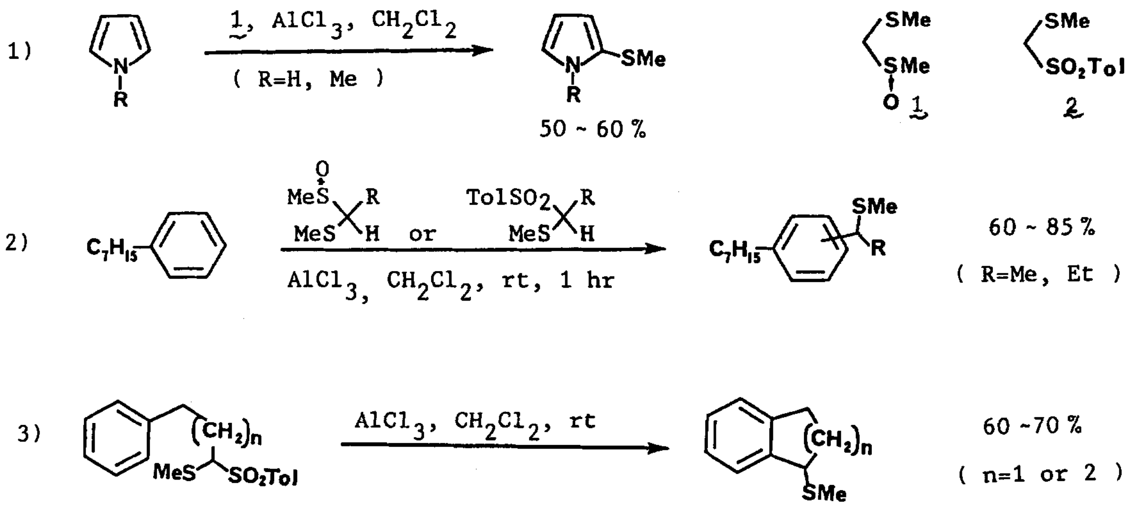
entry	R or substrates	method	temp(°C)/time(h)	isolated yield (%) (isomer ratio)[a]
1	H	A	rt/0.15	90
2	H	B	rt/0.15	90
3	CH_3	A	rt/0.15	80(o/p=1/4)
4	CH_3	B	rt/0.15	80(o/p=1/4)
5	$CH_2(CH_2)_5CH_3$	A	rt/0.15	80(o/p=1/7)
6	$CH_2(CH_2)_5CH_3$	B	rt/0.15	75(o/p=1/7)
7	$CH_2(CH_2)_5CH_3$	1/Me_3SiOTf	rt/3 days	65(o/p=1/4)[b]
8	$\underline{i}$-C_4H_9	A	0/0.5	85(o/p=1/5)
9	$\underline{s}$-C_4H_9	B	0/1	80(o/p=1/5)
10	$\underline{t}$-C_4H_9	A	rt/0.15	75(p)
11	$CH_2(CH_2)_2CH_2Br$	A	rt/0.15	70(o/p=1/4)
12	$CH_2(CH_2)_2OH$	B	rt/0.15	60(o/p=1/5)
13	$CH_2(CH_2)_2COOH$	B	rt/0.15	70(o/p=1/5)
14	OCH_3	B	-78/0.5	70(0/p=1/4)
15	$NHCOCH_3$	A	rt/7 days	70(o/p=1/5)
16	Cl	B	0/1	85(o/p=1/5)
17	Br	B	0/0.5	60(o/p=1/3)
18	I	A	rt/0.15	70(o/p=1/3)
19	Thiophene	A	-78/0.15	55(α)
20	N-Methylpyrrole	B	-78/0.15	50(α)
21	Ethyl 2-furoate	B	rt/1	80(α)
22	Naphthalene	B	rt/0.15	70(α)

a) The o/p ratio was determined by ^{1}H-NMR and GLC analysis.

b) The formation of byproducts was observed. Similar result was obtained when $TiCl_4$ was used as a Lewis acid.

Although other typical Lewis acids such as $SnCl_4$, $ZnCl_2$, alkylaluminum chlorides and so on were also examined, good reproduciable results were obtained in the case where catalysts as cited in the Table I were used. It was found that the preferable ratio of the reagent (**1** or **2**) to the Lewis acid for the best yields was 1:2.

Scheme I



In entry 1-13, no clear difference of yields between the methods (A) and (B) was observed, while in entry 14-22, a clear preference was seen, where only the result with the better yield is shown in Table I. In the reaction of pyrrole derivative (entry 20), normal MTM product was obtained by method B, while method A led to an unexpected product (Scheme I, eq.1).

It also should be noted that some functional groups which are sensitive under normal Friedel-Crafts conditions remained intact in these reactions (entrys 11, 12 and 13). Furthermore, considering the fact that well-known Vilsmeier-Haak formylation was completely ineffective to the non-activated benzene derivatives such as alkylbenzenes and benzene itself, the present methylthiomethylation is of great value in synthetic chemistry, especially for the introduction of the C$_1$-unit into relatively unreactive aromatic skeletons.

As an extention of this methodology, we next examined the possibility of other α-thioalkylation reactions using these sulfur templates. All the substrates examined (Scheme I) were easily prepared by treatment of **1** or **2** with bases (n-BuLi etc.) followed by the addition of the proper electrophiles. It was found that under similar reaction conditions to the MTM case, the AlCl$_3$-promoted α-thioalkylation took place quite easily as shown in Scheme I. To our delight, both intermolecular (eq.2) and intramolecular (eq.3) reactions were possible in the typical examples.

In conclusion, we have demonstrated that under proper conditions, sulfoxide and sulfone work as good leaving groups by the aid of a Lewis acid to promote electrophilic aromatic substitutions. Reactions with other nucleophilic counterparts will be possible and are currently investigated.

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References and Notes

1) H.Gross and G.Matthey, Chem. Ber., 1964, **97**, 2606.
2) Y.Tamura and H.Ishibashi, J. Synth. Org. Chem. Japan, 1982, **40**, 58.
3) I.K.Stamos, Tetrahedron Lett., 1985, **26**, 2787.
4) D.J.R.Massy, Synthesis, 1987, 589.
5) K.Ogura and G.Tsuchihashi, Tetrahedron Lett., 1972, 2681; K.Ogura, M.Suzuki, and G.Tuchihashi, Bull. Chem. Soc. Jpn., 1980, **53**, 1414.
6) K.Ogura, T.Tsuruda, K.Takahashi, and H.Iida, Tetrahedron Lett., 1986, **31**, 3665 and other references cited therein.
7) B.M.Trost and M.R.Ghadiri, J. Am. Chem. Soc., 1984, **106**, 7260; K.C.Nicolaou, M.E.Duggan, and C.K.Hwang, ibid., 1986, **108**, 2468; B.M.Trost and G.K.Mikhail, ibid., 1987, **109**, 4124, and other references cited therein.
8) Typical experimental procedures are as follows: To an orange suspension of $AlCl_3$ (530 mg, 4 mmol, well-crushed and heated under vacuum) in CH_2Cl_2 (4 ml) was added **1** (0.2 ml, 2 mmol) or **2** (430 mg, 2 mmol) at room temperature. A slightly exsothermic reaction took place and a nearly clear solution was obtained. The mixture was kept in the appropriate temperature as shown in the Table I, and the aromatic substrate (1mmol, neat or in CH_2Cl_2 solution) was then added to this solution. Stirring was kept for the time as indicated in the Table I. After reaction was complete, the mixture was diluted with ether and aq. $NaHCO_3$ to obtain a clear organic layer. Ether extracts was washed with brine and dried over $MgSO_4$ or Na_2SO_4. Crude material obtained after evapolation of solvent was further purified by silica-gel column chromatography using ether-hexane as eluent.

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