Communications to the Editor

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NEW METHODS AND REAGENTS IN ORGANIC SYNTHESIS. 46.[1] TRIMETHYLSILYLDIAZOMETHANE: A CONVENIENT REAGENT FOR THE O-METHYLATION OF PHENOLS AND ENOLS

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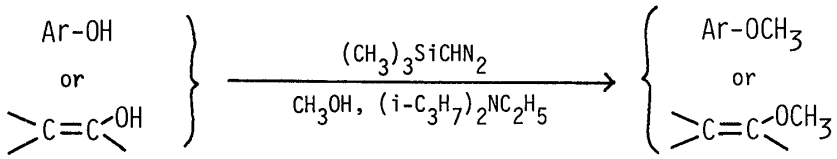
Trimethylsilyldiazomethane reacts smoothly with phenols and enols in methanolic acetonitrile solution in the presence of N,N-diisopropylethylamine to give methyl ethers.

KEYWORDS —— trimethylsilyldiazomethane; phenol; enol; O-methylation; methyl ether

Diazomethane is a well-known reagent for the methylation of phenols and enols.[3] However, this reagent is highly toxic and potentially explosive and should be handled with great care.

We have already reported that trimethylsilyldiazomethane ($TMSCHN_2$, $(CH_3)_3SiCHN_2$), as a stable and safe substitute for hazardous diazomethane, is quite useful as a reagent for introducing a C_1-unit.[4] As an extension of these works, we now wish to report that $TMSCHN_2$ can be used for the O-methylation of phenols and enols.

We have found that $TMSCHN_2$ reacts smoothly with phenols and enols at room temperature in methanolic acetonitrile solution in the presence of N,N-diisopropylethylamine to give the corresponding methyl ethers.



A typical experimental procedure is as follows (run 1 in Table): $TMSCHN_2$[5] (2.2 M hexane solution, 0.64 ml, 1.4 mmol) was added to a stirred solution of 2-naphthol (144 mg, 1 mmol) and N,N-diisopropylethylamine (180 mg, 1.4 mmol) in methanol-acetonitrile (1:9, 4 ml) at room temperature. The mixture was stirred for 15 h at room temperature, and concentrated in vacuo. The residue was worked up in the usual extractive manner to give 2-methoxynaphthalene (158 mg, 100%), mp 69-71°C, (Lit.,[6] mp 71°C).

The results are summarized in the Table. Various phenols including

Table. O-Methylation of Phenols and Enols with $TMSCHN_2$[a)]

Run	Starting material	Yield of product,%	Run	Starting material	Yield of product,%
1	2-Naphthol	100	12	2'-Hydroxyacetophenone	13
2	2,4-Dimethylphenol	58[b)]	13	Estrone	38[c,e)]
3	2-t-Butyl-5-methylphenol	31[c)]	14	4-Hydroxyquinoline	55[f)]
4	4-Phenylphenol	91	15	8-Hydroxyquinoline	61[c)]
5	2-Methoxyphenol	85[d)]	16	1-Phenyl-5-hydroxy-1,2,3-triazole	55
6	4-Methoxyphenol	93			
7	4-Bromophenol	71	17	Ethyl benzoylacetate	89[g)]
8	4-Nitrophenol	93	18	α-Methylsulfonyl-acetophenone	88[c,g)]
9	4-Hydroxybenzylalcohol	83			
10	Methyl 4-hydroxybenzoate	93	19	Benzoylacetone	77[h)]
11	Methyl salicylate	78			

a) Unless otherwise stated, the reaction was carried out as a typical procedure. All new compounds gave satisfactory elemental analyses and spectral data. b) Reaction time was 22 h. c) Reaction time was 18 h. d) Reaction time was 16 h. e) Starting material was recovered in 62% yield. f) 1-Methyl-4-quinolone(38%) was also obtained. g) Only the (Z)-isomer was formed; it was identified by TLC analysis and NMR spectra. h) A mixture of 3-methoxy-1-phenyl-2-buten-1-one (42%) and 4-methoxy-4-phenyl-3-buten-2-one (35%) was obtained.

heterocyclic ones smoothly undergo the O-methylation. 4-Hydroxybenzylalcohol and estrone give the corresponding methyl ethers without any change of their alcoholic hydroxyl and ketone functions, respectively. Reaction of 8-hydroxyquinoline with diazomethane has been described[3a)] to give 1-methyl-8-hydroxyquinolinium betaine with a small amount of 8-methoxyquinoline, but the methylation with $TMSCHN_2$ affords 8-methoxyquinoline in good yield. Readily enolizable ketones, such as ethyl benzoylacetate, α-methylsulfonylacetophenone, and benzoylacetone, also react with $TMSCHN_2$ to give the corresponding methyl enol ethers. Methanol as well as N,N-diisopropylethylamine seem to be essential to conduct the reaction smoothly. However, methanol is not a methylating agent in this reaction, since the increase of $[M+1]^+$ peak is not observed in the mass spectrum of 2-methoxynaphthalene when the O-methylation is carried out by the use of [^{13}C]methanol in place of usual methanol.

The present method is easy to conduct, appears to be general, and will provide a useful methodology for the O-methylation of both phenols and enols.

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