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NEW METHODS AND REAGENTS IN ORGANIC SYNTHESIS. 8.[1] TRIMETHYLSILYLDIAZOMETHANE. A NEW, STABLE, AND SAFE REAGENT FOR THE CLASSICAL ARNDT-EISTERT SYNTHESIS

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Stable and safe trimethylsilyldiazomethane(TMSCHN$_2$) can be used efficiently for the Arndt-Eistert synthesis in place of highly toxic and explosive diazomethane.

The Arndt-Eistert synthesis[2] is a well-known method for converting a carboxylic acid into a derivative of its next higher homolog. However, one of the serious disadvantages in this classical synthetic procedure is the use of diazomethane, because it is not only highly toxic but also explosive and hence should be very carefully handled. To our knowledge, no industrial use has been conducted

We now wish to propose the use of trimethylsilyldiazomethane(TMSCHN$_2$)[3] as a stable and safe substitute for very hazardous diazomethane in the Arndt-Eistert synthesis. TMSCHN$_2$ is known to be a thermally stable compound due to the C-Si pπ-dπ resonance.[3] We have found that TMSCHN$_2$ is easily acylated with a carboxylic acid chloride and the thermal treatment of the acylated product in the presence of benzyl alcohol smoothly gives a benzyl ester of a homologated carboxylic acid:

$$\mathrm{RCOCl} \xrightarrow[\text{2) } \mathrm{C_6H_5CH_2OH}]{\text{1) } \mathrm{(CH_3)_3SiCHN_2}} \mathrm{RCH_2CO_2CH_2C_6H_5}$$

A typical experimental procedure for the new Arndt-Eistert synthesis is as follows(run 5): To a mixture of TMSCHN$_2$(3 mM)[4] and triethylamine(303 mg, 3 mM) in tetrahydrofuran-acetonitrile(1:1, 10 ml) was added 1-naphthoyl chloride(458 mg, 2.4 mM) at 0°. The mixture was stirred at 0° for 30 hours, and evaporated in vacuo. Benzyl alcohol(2 ml) and 2,4,6-trimethylpyridine(2 ml) were added to the evaporated residue, and the mixture was stirred at 180-185° for 7 minutes. Benzene was added and the mixture was successively washed with 10 % aqueous citric acid, water, and saturated aqueous sodium chloride. After the mixture was dried over anhydrous magnesium sulfate, the solvent and an excess of benzyl alcohol were evaporated in vacuo. The oily residue was purified by a silica gel(Mallinckrodt Silic AR CC-7 special) column chromatography using benzene-hexane-diethyl ether(10:20:1) as eluate to give benzyl 1-naphthylacetate as a pale yellow oil (516 mg, 77.8 %).

Table. The Arndt-Eistert Synthesis Using Trimethylsilyldiazomethane($TMSCHN_2$)

Run	RCOCl	Reaction time for acylation(hr)	% Isolated yield of $RCH_2CO_2CH_2C_6H_5$[a]
1	Benzoyl chloride	24	62.8
2	4-Methoxybenzoyl chloride	48	60.2
3	4-n-Butoxybenzoyl chloride	48	75.8
4	4-Chlorobenzoyl chloride	24	66
5	1-Naphthoyl chloride	30	77.8
6	Thiophene-2-carbonyl chloride	48	64.4
7	3-Phenylpropionyl chloride	4	72.4
8	Cyclohexanecarbonyl chloride	6	58.5
9	(S)-N-Benzyloxycarbonylpyrrolidine-2-carbonyl chloride[b]	5	77.4[c]

[a] *All compounds were fully characterized by IR and NMR spectral methods and hydrolyzed with alkali to give known free acids.*

[b] *Prepared from N-benzyloxycarbonyl-L-proline according to the literature: J.-M. Cassal, A. Fürst, and W. Meier, Helv. Chim. Acta, 59, 1917(1976).*

[c] *Based on N-benzyloxycarbonyl-L-proline.*

The utility of the procedure is well demonstrated in Table. Various aromatic acid chlorides(runs 1-6) efficiently react with $TMSCHN_2$ at 0° during 24-48 hours in tetrahydrofuran-acetonitrile(1:1) in the presence of triethylamine. Aliphatic and alicyclic acid chlorides(runs 7-9) require 2 equivalents of $TMSCHN_2$ and the acylation reaction proceeds at 0° within several hours without triethylamine. The crude acylated products easily undergo the Wolff rearrangement in the presence of benzyl alcohol and 2,4,6-trimethylpyridine at 180-185° for 7 minutes to give benzyl esters of homologated acids.

$TMSCHN_2$ may replace diazomethane and create added flexibility in synthesis.

REFERENCES AND NOTES

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3 D. Seyferth, H. Menzel, A.W. Dow, and T.C. Flood, J. Organomet. Chem., 44, 279 (1972); See also T.J. Barton and S.K. Hoekman, Synth. React. Inorg. Metal-Org. Chem., 9, 297(1979).

4 $TMSCHN_2$ was prepared by the Seyferth's method,[3] which we slightly modified. The actual reagent used has been a mixture of $TMSCHN_2$ and hexamethyldisiloxane (7:3), the latter of which has no influence on the reaction.

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