A New Method of Methoxymethylation

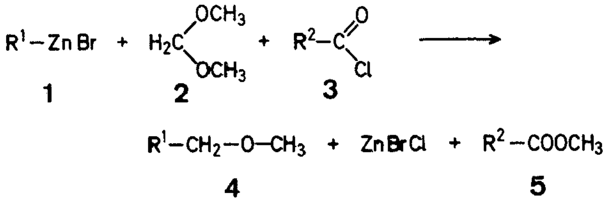
François Dardoize, Marcel Gaudemar, Nicole Goasdoué

Laboratoire de Synthèse Organométallique, Université P. et M. Curie, Bâtiment F. 4, Place Jussieu, F-75230 Paris Cedex 05, France

The methoxymethyl group is a commonly used protective group for phenols, carboxylic acids, and carboxamides[1,2,3]. A recent report[4] on the introduction of this group prompts us to publish our own simple and efficient method which we employ since a few years.

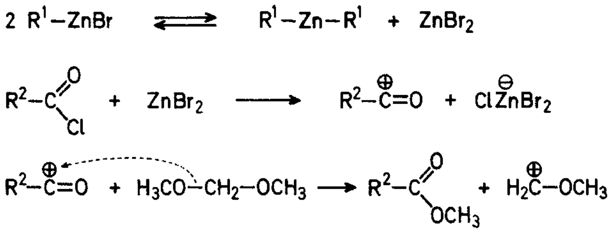
Literature preparations of *O*-, *S*-, and *N*-methoxymethyl derivatives generally involve the reaction of an anion with chloromethyl methyl ether. Our method and the one reported in Ref.[4] use dimethoxymethane (methylal) as source of the methoxymethyl cation and thus avoid the use of chloromethyl methyl ether (which is carcinogenic).

Our observation[5] that the reaction of alkyl- and alkoxyzinc bromides (**1**) with acetyl chloride (**3**, $R^2 = CH_3$) in dimethoxymethane (**2**) leads to the conversion of the zinc derivative **1** into a methoxymethyl derivative (**4**) instead of the formation of methoxymethyl acetate suggested a new methoxymethylation method which may be formulated as follows.



$$R^1\text{-}ZnBr + H_2C(OCH_3)_2 + R^2\text{-}COCl \longrightarrow R^1\text{-}CH_2\text{-}O\text{-}CH_3 + ZnBrCl + R^2\text{-}COOCH_3$$

In this method, the zinc derivatives **1** are prepared from acidic compounds R^1—H and an easily accessible organozinc reagent such as ethyl bromozincoacetate ($BrZn—CH_2—COOC_2H_5$). The formation of the methoxymethyl cation which is operative in the above reaction may rationalized by the following sequence.

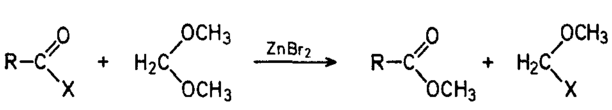


$$2\,R^1\text{-}ZnBr \rightleftharpoons R^1\text{-}Zn\text{-}R^1 + ZnBr_2$$

$$R^2\text{-}COCl + ZnBr_2 \longrightarrow R^2\text{-}\overset{\oplus}{C}{=}O + Cl\overset{\ominus}{Zn}Br_2$$

$$R^2\text{-}\overset{\oplus}{C}{=}O + H_3CO\text{-}CH_2\text{-}OCH_3 \longrightarrow R^2\text{-}COOCH_3 + H_2\overset{\oplus}{C}\text{-}OCH_3$$

This assumption is supported by the fact that the reaction of equimolar amounts of an acyl halide (X = Cl, Br, J) with dimethoxymethane in the presence of catalytic amounts of zinc bromide affords the corresponding methyl carboxylate and halomethyl methyl ether.



$$R\text{-}COX + H_2C(OCH_3)_2 \xrightarrow{ZnBr_2} R\text{-}COOCH_3 + H_2C(OCH_3)X$$

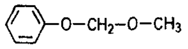
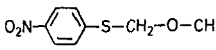
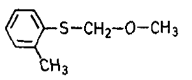
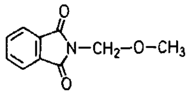
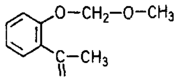
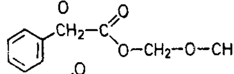
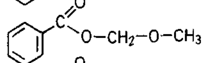
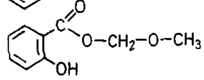
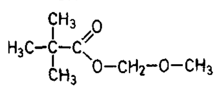
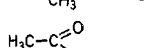
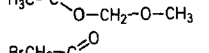
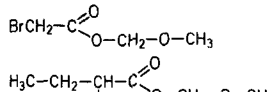
This method of synthesis of methyl carboxylates and halomethyl methyl ethers is the subject of a forthcoming publication.

The following procedure is typical.

Methoxymethyl Benzoate (**4**, $R^1 = C_6H_5—CO—O—$):

In a 500-ml three-necked flask fitted with a stirrer, an addition funnel, and a thermometer, zinc (6.5 g, 0.1 mol) is covered with dimethoxymethane (20 ml) and activated by addition of a few drops of pure ethyl bromoacetate. The temperature rises to 40° and the reflux is maintained by addition of a solution of ethyl bromoacetate (16.7 g, 0.1 mol) in dimethoxymethane (40 ml). At the end of the addition the mixture is heated until the zinc disappears (~30 min). To this stirred solution is added dropwise a solution of benzoic acid (9.77 g, 0.08 mol) in dimethoxymethane (15 ml). The H/M exchange is followed by I.R. After the reaction is complete the mixture is cooled to −5° and acetyl chloride (5.0 g,

Table. Methoxymethyl Derivatives (**4**) obtained from Acidic Compounds R^1-H via Their Zinc Bromide Derivatives (**1**)

4	Yield[a] [%]	b.p. or m.p.	Lit. b.p. or m.p. or Molecular formula	^{1}H-N.M.R. (CDCl$_3$) δ [ppm] $-O-CH_2-$	$-O-CH_3$
	72	b.p. 74°/15 torr	b.p. 63–65°/8 torr[6]	5.08	3.40
	80	b.p. 110°/0.05 torr	$C_8H_9NO_3S$ (199.2)[b]	5.02	3.40
	82	b.p. 113°/12 torr	$C_9H_{12}OS$ (168.2)[b]	4.9	3.40
	62	m.p. 120° (ethanol)	m.p. 120–121°[7]	5.1	3.40
	45	b.p. 130°/12 torr	$C_{10}H_{12}O_3$ (180.2)[b]	5.25	3.48
	85	b.p. 73°/0.1 torr	$C_{10}H_{12}O_3$ (180.2)[b]	5.20	3.34
	76	b.p. 110°/12 torr	$C_9H_{10}O_3$ (166.2)[b]	5.45	3.50
	78	b.p. 65°/0.01 torr	b.p. 153°/32 torr[8]	5.52	3.55
 $(CH_3)_3C-CO-O-CH_2-O-CH_3$	79	b.p. 45°/12 torr	$C_7H_{14}O_3$ (146.2)[b]	5.20	3.42
 $H_3C-CO-O-CH_2-O-CH_3$	68	m.p. 117°	$C_4H_8O_3$ (104.1)[b]	5.10	3.38
 $BrCH_2-CO-O-CH_2-O-CH_3$	80	b.p. 79°/11 torr	$C_4H_7BrO_3$ (183.0)[b]	5.22	3.45
 $H_3C-CH_2-CH(Br)-CO-O-CH_2-O-CH_3$	88	b.p. 90°/13 torr	$C_6H_{11}BrO_3$ (211.1)[b]	5.22	3.42
	56[c]	b.p. 106°/12 torr	$C_{10}H_{10}O$ (146.2)[b]	4.20	3.35

[a] Yield of isolated pure product; the yields are not optimized.

[b] New compounds. The microanalyses showed the following maximum deviations from the calculated values: C, ±0.1%; H, ±0.3%; Br, ±0.5%; S, ±0.35%.

[c] 40% unreacted phenylacetylene was recovered.

0.08 mol) is added dropwise (with stirring) at such a rate that the temperature does not exceed 0°. Stirring is continued for 2 h and the temperature allowed to reach 20–25°. Then, a 1:1 mixture (200 ml) of conc. aqueous ammonia and saturated aqueous ammonium chloride is added. The mixture is extracted with ether (3 × 100 ml), the extract washed with saturated sodium chloride solution, and dried with magnesium sulfate. The solvent is evaporated and the residue distilled in vacuo; yield: 12.2 g (76%); b.p. 110°/12 torr.

Methyl Benzoate:

A solution of benzoyl chloride (0.1 mol) and anhydrous zinc bromide (2.0 g) in dimethoxymethane (60 ml) is stirred at 44° for 6 h. The mixture is poured into cold water (300 ml), extracted with ether (3 × 100 ml), and dried with magnesium sulfate. The ether is evaporated and the residue distilled to give methyl benzoate; yield: 12.8 g (94%).

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[8] *German Patent (DRP)* 137 585 (1902), Bayer & Co.: *Chem. Zentralblatt* **1903** I, 112.