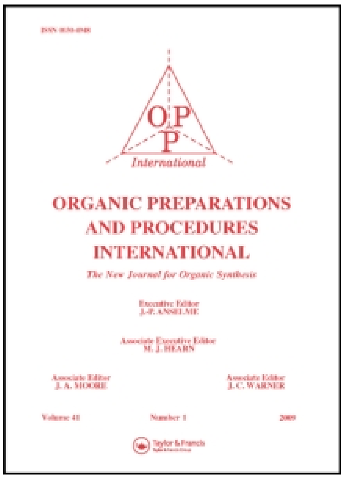

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Richard A. Bunce[a]; A. Joe Shellhammer Jr.[a]
[a] Department of Chemistry, Oklahoma State University, Stillwater, Oklahoma

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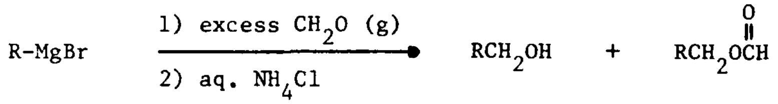
FORMATE ESTERS BY CANNIZZARO-TISHCHENKO REACTION OF GRIGNARD AND SODIUM ALKOXIDES WITH FORMALDEHYDE

Richard A. Bunce* and A. Joe Shellhammer Jr.[†]
Department of Chemistry, Oklahoma State University,
Stillwater, Oklahoma 74078-0447

Recent synthetic studies in this laboratory required the one-carbon homologation of alkyl halides by reaction of their Grignard reagents (1) with formaldehyde. In the course of this work, it was noted that reaction of these organometallic derivatives with an excess of gaseous formaldehyde in refluxing tetrahydrofuran yielded varying amounts of a carbonyl-containing product in addition to the expected alcohol (2). Spectral analysis of this product revealed it to be the formate ester (3) of the desired chain-extended alcohol (see eq. 1).

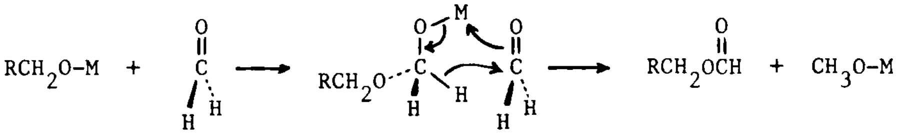


$$\underset{1}{\text{R-MgBr}} \xrightarrow[\text{2) aq. } NH_4Cl]{\text{1) excess } CH_2O\text{ (g)}} \underset{2}{RCH_2OH} + \underset{3}{RCH_2O\overset{\overset{O}{\|}}{C}H} \qquad (1)$$

This reaction has been explored further to improve yields of the alcohol product and possibly to develop a new general route to formate esters.

The present study has shown that ester contamination is difficult to prevent in Grignard reactions using gaseous formaldehyde due to problems in regulating the uptake. Paraformaldehyde is more easily measured but generally is not favored for the reaction in low boiling solvents since depolymerization occurs too slowly at temperatures below 100 °C.[1] The current procedure involves bubbling formaldehyde gas directly into a refluxing solution containing the Grignard reagent. This typically results in the isolation of alcohol 2 contaminated with 5-25% of the corresponding formate ester 3. An alternative technique, wherein formaldehyde gas is passed over the surface of the reaction mixture, was found to give better yields of the alcohol with less of the ester impurity. In either case, contamination of the crude alcohol by the formate does not limit this homologation procedure since the ester can be readily hydrolyzed to the alcohol with mild base.[2]

Experimental evidence suggests that the mechanism by which formate esters arise parallels that known for the Cannizzaro-Tishchenko process (see eq. 2). This requires the formation of one equivalent of methoxide for each molecule of ester generated. The presence of methoxide has been verified by gas chromatographic detection of methanol and methyl formate in a water-quenched aliquot of the crude reaction mixture.



(2)

M = MgBr
M = Na

The present study was undertaken to explore the possibility of optimizing this reaction as a general synthesis of formate esters. Several representative formates, prepared by the Cannizzaro-Tishchenko reaction, are given in the Table. Primary, secondary and tertiary alkoxides, generated by Grignard addition to a carbonyl compound or by base-induced (EtMgBr or NaH) deprotonation of an alcohol, were all converted to formate esters by reaction with a four- to five-fold excess of gaseous formaldehyde in refluxing THF. The reaction does not seem to be limited by steric factors and side reactions, such as elimination, were not observed. Temperature control, however, appears to be critical to the process with THF (bp. 67

should prove intermediate in utility relative to known methods. Compared to the Fischer esterification, the Cannizzaro-Tishchenko approach can be applied to a broader range of substrates but has similar limitations in producing product of only 90-97% purity.[3] On the other hand, the current method cannot match the high purity esters isolated from reactions of formic acetic anhydride or formic acid-acetic anhydride-pyridine with alcohols.[4] Nevertheless, the reaction should prove useful since the reaction is general, it is fast and it does not require isolation of the alcohol from Grignard mixtures.

In summary, formate esters can be prepared by reaction of Grignard reagents with gaseous formaldehyde. Ester formation apparently arises from a Cannizzaro-Tishchenko reaction of the bromomagnesium alkoxides with excess formaldehyde. The reaction can be extended to sodium alkoxides as well. Experimental conditions are described which make this procedure a general source of formate esters.

EXPERIMENTAL SECTION

Paraformaldehyde (Eastman) was dried over P_2O_5 under vacuum at room temperature for 48 h prior to use. THF was predistilled from CaH_2 and finally distilled from sodium benzophenone ketyl. GC measurements were made using a Varian 3400 capillary GC with FI detection (0.25 mm X 3 m DB-1 column at 50 °). IR spectra were recorded with a PE-681 instrument and are referenced to polystyrene. PMR spectra were measured as solutions in $CDCl_3$ using a Varian XL-300 superconducting FT instrument; chemical shifts are reported in δ units relative to internal Me_4Si. Mass spectra were recorded at 70 eV using a CEC double focusing mass spectrometer.

<u>General Procedure for Formate Ester Preparation from Alkoxides</u>.- Into a solution (or suspension) of 0.1 mol of the alkoxide in 100 mL of refluxing THF was bubbled gaseous formaldehyde generated by 150 ° pyrolysis of 12-15 g (ca. 0.4-0.5 mol) of anhydrous paraformaldehyde. The mixture was cooled and worked up with saturated aqueous ammonium chloride and ether at 0 °; if a precipitate or an emulsion was formed upon cooling

Table. Formates Prepared by Reaction of Grignard and Sodium Alkoxides with Formaldehyde.

Alkoxide From	Metal	Procedure[a]	% Yield[b] (GC Purity)
benzyl alcohol	MgBr	A	76[c] (95)
cyclohexylmethanol	MgBr	B	60 (92)
heptyl alcohol	MgBr	A	63[c] (93)
	MgBr	B	74[c] (97)
	Na	C	85[c] (97)
3-phenylpropanol	MgBr	B	69[c] (95)
3-methyl-3-phenyl-butanol	MgBr	A	85 (95)
3,3,5-trimethyl-cyclohexanol	MgBr	A	82 (93)
	Na	C	83 (94)
2-phenyl-2-propen-1-ol	MgBr	B	63 (92)
1-ethylcyclohexanol	MgBr	D	75 (90)

(a) Procedure A indicates deprotonation of the alcohol by EtMgBr; Procedure B indicates preparation of the alkoxide by addition of the appropriate Grignard reagent to formaldehyde; Procedure C indicates deprotonation of the alcohol by NaH; Procedure D indicates preparation of the alkoxide by addition of EtMgBr to cyclohexanone. (b) Isolated yields. (c) Spectral data for these compounds matched those found in the Sadtler Index.

°C) being superior to diethyl ether and di-*n*-butyl ether. It was also noted that complete solubility of the alkoxide was not a requirement; several of the bromomagnesium alkoxides and all of the sodium alkoxides were heterogeneous dispersions in THF. Finally, the fact that both sodium and bromomagnesium alkoxides afford similar results rules out the necessity for having Lewis acids such as $MgBr_2$ or MgBrOR present in the reaction mixture.

It is envisioned that the present procedure will have general application as a means for converting alkyl halides directly into homologated formate esters. As a method for esterifying alcohols, this technique or quenching, the mixture was filtered through Celite® and the residue was washed with THF, saturated ammonium chloride and THF prior to standard workup. The combined organic layer was washed at 0 ° with water and saturated sodium chloride, dried by filtration through a plug of anhydrous sodium sulfate, concentrated and vacuum distilled. The following new compounds were prepared:

Cyclohexylmethyl Formate: bp. 60-62 ° at 8 mm Hg (lit.[5] bp. 49-51 ° at 3.5 mm Hg); IR (neat) 1730, 1172 cm^{-1}; PMR δ 8.12 (s, 1H), 3.99 (d, 2H, J = 7 Hz), 1.74 (m, 7H), 1.23 (m, 4H); MS, m/z (relative intensity) 142 (M^+, 4), 97 (100), 96 (35), 45 (15); exact mass calcd for $C_8H_{14}O_2$, m/z 142.0994, found m/z 142.0963.

3-Methyl-3-phenylbutyl Formate: bp. 85-87 ° at 1 mm Hg; IR (neat) 1730, 1388, 1367, 1170 cm^{-1}; PMR δ 8.02 (s, 1H), 7.43 (m, 5H), 4.09 (t, 2H, J = 7 Hz), 2.13 (t, 2H, J = 7 Hz), 1.46 (s, 6H); MS, m/z (relative intensity) 192 (M^+, 5), 146 (2), 131 (28), 120 (25) 119 (100), 91 (69), 45 (12); exact mass calcd for $C_{12}H_{16}O_2$, m/z 192.1150, found m/z 192.1147.

3,3,5-Trimethylcyclohexyl Formate: bp. 96-97 ° at 20 mm Hg; IR (neat) 1730, 1390, 1368, 1180 cm^{-1}; PMR δ 8.06 (s, 1H), 5.04 (m, 1H), 1.98 (m, 1H), 1.70 (m, 2H), 1.34 (m, 1H), 1.20-0.78 (complex, 12H); MS., m/z (relative intensity) 170 (M^+, 0.5), 125 (8), 124 (32), 110 (11), 109 (100), 95 (15), 83 (44), 82 (31), 45 (18); exact mass calcd for $C_{10}H_{18}O_2$, m/z 170.1307, found m/z 170.1299.

2-Phenyl-2-propenyl Formate: bp. 79-80 ° at 1.5 mm Hg; IR (neat) 1728, 1634, 1165, 778, 707 cm^{-1}; PMR δ 8.04 (s, 1H), 7.44 (m, 2H), 7.32 (m, 3H), 5.57 (s, 1H), 5.39 (s, 1H), 5.05 (s, 2H); MS, m/z (relative intensity) 162 (M^+, 0.4), 117 (100), 45 (51); exact mass calcd for $C_{10}H_{10}O_2$, m/z 162.0681 found m/z 162.0688.

1-Ethylcyclohexyl Formate: bp. 45-46 ° at 0.5 mm Hg; IR (neat) 1730, 1196

cm^{-1}; PMR δ 8.12 (s, 1H), 2.20-1.20 (complex, 10H), 1.93 (q, 2H, J = 7 Hz), 0.90 (t, 3H, J = 7 Hz); MS, m/z (relative intensity) 128 ($M^+-C_2H_4$, 12), 111 (100), 110 (16), 99 (63), 45 (51); exact mass calcd for $C_9H_{16}O_2-CHO_2$, m/z 111.1174, found m/z 111.1171.

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