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PREPARATION OF FUNCTIONALIZED KETONES VIA LOW TEMPERATURE GRIGNARD REACTION

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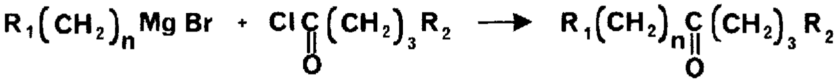
Abstracts: δ-Chloroketones and 5-oxo-9-decenoic acid methyl ester were prepared from 5-chlorovaleryl chloride and methyl 4-(chloroformyl)-butyrate via Grignard reaction in tetrahydrofuran at -70°.

The recent publication of a paper[1] in this journal concerning the subject of low temperature Grignard reactions prompts us to disclose our own experiments in this field. We became interested in the preparation of some hitherto unknown ketones bearing functions which could be susceptible to side reactions under the normal conditions for Grignard reactions.[2] We could find only few references pertaining to this technique. Darzens[3] carried out such a reaction at -10° on an acid chloride. Ketones were also prepared from acid anhydrides[4] at low temperature in the presence of Grignard reagents. Other acid chlorides[5] required a catalyst to suppress side reactions or were used with inverse addition.[6] All these references, except one,[6] call for ether as solvent.

When we attempted our first Grignard reaction between methyl 4-(chloroformyl)-butyrate and 1-bromo-4-pentene in ether at -70° we obtained the expected product in 20% yield accompanied by about 30% of material of higher molecular weight. When the same reaction was carried out in tetrahydrofuran we consistently obtained yields in the 60-80% range. However it was important to maintain the temperature below -67° during the addition of the acid chloride to the Grignard reagent.

In one of our earlier attempts the acid chloride was added too rapidly and the temperature rose from -50° to +30°C within a few seconds. (The reaction was discarded.) The structures of three δ-chloroketones, prepared from 5-chlorovaleryl chloride and the corresponding Grignard reagents at -65° to -70°C (internal temperature) are listed below. No inverse additions were employed.



$$R_1(CH_2)_nMgBr + Cl\underset{\underset{O}{\|}}{C}(CH_2)_3R_2 \longrightarrow R_1(CH_2)_n\underset{\underset{O}{\|}}{C}(CH_2)_3R_2$$

n	R_1	R_2	% yield[a]	Product[b] b.p./mm Hg	m/e $[M^+]$
3	CH_2=CH	$COOCH_3$	81	42-47°/0.11 (c)	198
3	CH_2=CH	CH_2Cl	72	80-85°/0.2	188
4	CH_2=CH	CH_2Cl	53	100°/0.65	202
2	CH_2=CH	CH_2Cl	65	75-80°/0.16	174
2	H	$COOCH_3$	74	130-150°/14 (c)	158

[a] Yield after dist.

[b] The products were characterized by nmr and ir spectra and gave satisfactory elemental analyses

[c] Kugelrohr dist.

5-Oxo-4-decenoic acid methyl ester. In a 3 lt flask equipped with condenser, dropping funnel, nitrogen inlet and an efficient mechanical stirrer, were placed 17.0 g (0.7 mol) of magnesium and 400 ml of dry tetrahydrofuran. Then 100 ml of a solution of 100.0 g (0.67 mol) of commercial 5-bromo-1-pentene in 400 ml of THF was added. After the reaction had started (∿3-5 min.), the remainder of the solution was added at a rate to maintain gentle reflux. Heating was continued for 3 additional hours. The mixture was cooled in an acetone/dry ice bath. A solution of 111.0 g (0.67 mol) of methyl 4-(chloroformyl)-butyrate was added, with vigorous stirring, at a rate to maintain the temperature below -67°C. The mixture was allowed to warm to room temperature together with the bath (stirring overnight), poured on ice/NH_4Cl and separated. The aqueous phase was extracted with ether. The combined organic layers were dried over Na_2SO_4. Evaporation of the solvent left the product as an amber liquid which was distilled in a Kugelrohr; yield 107.8 g (81%); b.p. 42-47°/0.11 mm Hg.

References:

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