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ONE-STEP SYNTHESIS OF KETONES FROM CARBOXYLIC ACIDS AND GRIGNARD REAGENTS IN THE PRESENCE OF A NICKEL(II)-PHOSPHINE CATALYST.

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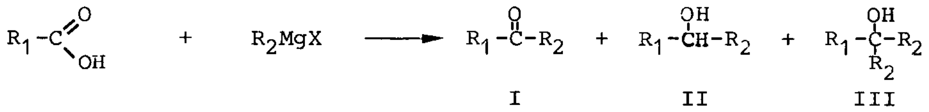
Summary: A one-step synthesis of diaryl and alkyl-aryl ketones by the reaction of carboxylic acid with Grignard reagents in the presence of $NiCl_2(Ph_2PCH_2CH_2PPh_2)$ as catalyst is described. In the nickel-catalyzed Grignard reaction the formation of alcohols is nearly completely suppressed.

It is known that the reaction of Grignard reagents with carboxylic acids cannot be used for one-step synthesis of ketones because low yields and simultaneous formation of secondary and/or tertiary alcohols are obtained[1]. Some reports of higher yields of ketones from carboxylic acids and organolithium reagents can be found in the literature[2]. However, except with methyllithium[3], the method results also in the formation of carbinols and, generally, precautionary measures in mixing the reagents and a careful work-up procedure are required in order to minimize the formation of side products. Yields of ketones can also be improved by using the lithium salt of carboxylic acids[2a,4], though this procedure is plagued with the preparation and drying of the lithium salt of the acid to be used, which adds another synthetic step to the reaction sequence. Therefore, generally, carboxylic acid derivatives were preferred in the reactions with organometallic reagents for ketones synthesis[5].

In the last decade it has been shown extensively that the course of Grignard reactions in the formation of C-C bond with several unsaturated compounds is markedly influenced by the presence of nickel or palladium complexes as catalysts[6]. Our interest in this field[7] prompted us to extend the nickel-catalyzed Grignard reaction to carboxylic acids with the aim of minimizing the formation of alcohols to an extent which would make the ketone production synthetically useful. Indeed, in a recent spectroscopy study[8] of the 3,5-diisopropylsalicylic acid/n-BuMgBr system in the presence of Ni(II), an increase of the amount of the keto product was observed by ^1H NMR, using an acid/$NiCl_2$ molar ratio equal to ten or starting with the nickel salt of the carboxylic acid.

We can now report that in the presence of $Ni(dppe)Cl_2$ as catalyst, (dppe = $Ph_2PCH_2CH_2PPh_2$), in the reaction of Grignard reagents with carboxylic acids the production of alcohols is nearly completely suppressed, and ketones can be isola-

TABLE



$$R_1-COOH + R_2MgX \longrightarrow \underset{\textbf{I}}{R_1-\overset{O}{\overset{\|}{C}}-R_2} + \underset{\textbf{II}}{R_1-\overset{OH}{\overset{|}{C}H}-R_2} + \underset{\textbf{III}}{R_1-\overset{OH}{\overset{|}{\underset{R_2}{\underset{|}{C}}}}-R_2}$$

Entry	R_1	R_2	Reaction Conditions		ratio %			Yield in ketone[b] %
			catalyst[a]	t h	I	II	III	
1	C_6H_5	n-C_5H_{11}	Ni(dppe)Cl_2	24	92	3	5	75
2		n-C_5H_{11}	None	24	16	8	76	
3		n-C_4H_9	Ni(dppe)Cl_2	24	95	3	2	65
4		n-C_4H_9	None	24	10	10	80	
5		C_6H_5	Ni(dppe)Cl_2	24	98	1	1	60
6		C_6H_5	None	24	69	1	30	
7	m-CH_3-C_6H_4	n-C_5H_{11}	Ni(dppe)Cl_2	24	91	4	5	65
8		n-C_5H_{11}	None	24	19	5	76	
9		n-C_4H_9	Ni(dppe)Cl_2	24	93	4	3	60
10		n-C_4H_9	None	24	16	7	77	
11		C_6H_5	Ni(dppe)Cl_2	24	96	0	4	60
12		C_6H_5	None	24	80	0	20	
13	2-Np[c]	C_6H_5	Ni(dppe)Cl_2	24	91	4	5	70
14		C_6H_5	None	24	18	10	72	
15	$CH_3(CH_2)_2$	C_6H_5	Ni(dppe)Cl_2	72	93	2	5	70
16		C_6H_5	None	72	16	1	83	
17	$CH_3(CH_2)_3$	C_6H_5	Ni(dppe)Cl_2	72	93	2	5	65
18		C_6H_5	None	72	10	1	89	
19	$CH_3(CH_2)_4$	C_6H_5	Ni(dppe)Cl_2	72	92	3	5	60
20		C_6H_5	None	72	14	1	85	
21	$CH_3(CH_2)_3$	n-C_4H_9	Ni(dppe)Cl_2	72	86		14	40[d]
22		n-C_4H_9	None	72	20		80	

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[a] Molar ratio catalyst/RMgX was 1.5×10^{-2} in each case. [b] The yields are based on the starting carboxylic acid and refer to pure products isolated after short-path column chromatography and distillation or crystallization. In the case of entries 5, 11, 13, 15, 17 and 19 diphenyl formed as co-product was removed by silica gel column chromatography. [c] Np= naphthyl. [d] Yield based on GLC analysis. Work-up gave 50% recovery of starting carboxylic acid.

ted in satisfactory yields (see table). In all cases, except for entry 21, the amount of secondary and/or tertiary alcohols was less than 5%.[9] In contrast, when the same reactions were carried out in absence of the catalyst, tertiary alcohols were the main product and the yields of ketones were low.

As illustrated by the entries in the table, the procedure can be applied successfuly to the synthesis of diaryl and alkyl-aryl ketones with isolated yields in the range 60-75%. However, the acid/Grignard reagent molar ratio appears to play an important role since complete conversion of carboxylic acid to ketone required six equivalents of Grignard reagent. In fact with a 1/3 acid/Grignard reagent molar ratio, even after rather long reaction times, 50% of the starting acid could be recovered together with the products. A similar incomplete conversion of carboxylic acid was also observed in the reaction between aliphatic carboxylic acids and alkyl Grignard reagents in a 1/6 molar ratio (entry 21).

The following procedure for the synthesis of hexanophenone is representative. Ni(dppe)Cl$_2$ (0.14g, 2.7x10^{-4}mol) is added to a solution of benzoic acid (0.49g, 4x10^{-3}mol) in 40 ml dry THF. After stirring under N$_2$ for a few minutes at room temperature, *n*-pentylmagnesium bromide (29 ml of a 0.81 M solution in ether) is added dropwise. After an initial exothermic reaction, the resultant black mixture was allowed to stir for 24 h at room temperature. The reaction was then quenched by pouring the mixture into dilute hydrochloric acid and extracted with several portions of ether. The organic layer was washed with aq NaHCO$_3$, followed by water, and was dried over Na$_2$SO$_4$. After removal of the solvent, short-path column chromatography on silica gel, eluting with hexane/ether 9/1, gave almost pure hexanophenone[10] (90% GLC yield). The resulting crude product was distilled to give 0.53g of pure hexanophenone (75% yield).

In conclusion, although more work is needed to elucidate the role of the catalyst, the nickel-Grignard reaction appears generally more satisfactory than any of the known organometallic routes for converting carboxylic acid itself into ketone, in satisfactory yield and in one-step operation. We are presently investigating the synthetic potential of this procedure.

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9. The ratio was determined by GLC analysis on a DANI 3900 glass-capillary columns dedicated gas-chromatograph, using a Carbowax 20 M glass capillary column (30m x 0.25mm i.d.) and a FID detector (carried gas He, 0.6 bar; split 60 ml/min). The products were identified by comparison with authentic samples. Other unknown products were identified by IR, MS and ^{1}H NMR spectra.
10. This chromatography is necessary to remove secondary alcohol which is difficult to eliminate by distillation.

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