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Direct Ni° mediated Synthesis of Ketones from Acyl Bromides and Grignard Reagents

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Abstract: a catalytic amount of $NidppeCl_2$ converts an acyl bromide directly into ketones at 0 °C in THF in the presence of a Grignard reagent. The described procedure represents a useful way to afford dialkyl, diaryl or alkyl aryl ketones as well as 1,2-diketones. In the adopted reaction conditions double bonds, esters and ketones are unaffected.

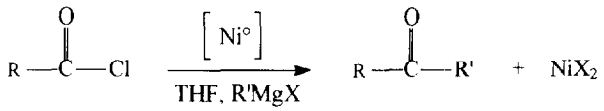
One of the most interesting functional group interconversion is represented by an acyl halide-ketone transformation step, but the reaction seems to be useful only if soft organometallic species, often prepared from the corresponding Grignard reagents, are employed[1].

Some transition metal catalysts can be used to mediate the reaction, such as $Pd(PPh_3)_4$ and $RZnX$[2], $ClRh(PPh_3)_3$ and SnR_4[3], $Cu(acac)_2$ and R_3Al[4] or $Fe(acac)_3$ and $RMgX$[5]. On the other hand, when Grignard reagents are used, very low temperatures, particular solvents and high excess of the halide have to be employed[6].

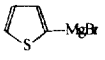
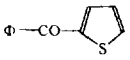
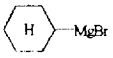
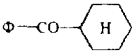
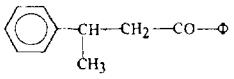
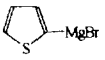
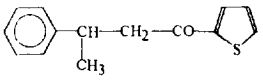
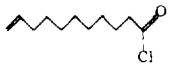
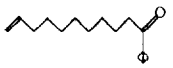
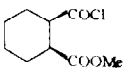
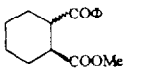
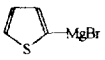
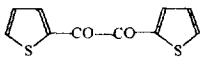
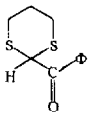
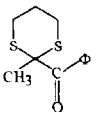
The literature gives a few examples in which Ni° compounds are used in stoichiometric[7] or catalytic[8] amounts respectively.

During our studies on the nickel organic chemistry, we took into consideration the possibility to afford ketones starting directly from Grignard reagents and acyl halides, by using $NidppeCl_2$ as catalyst (Scheme 1)

Scheme 1



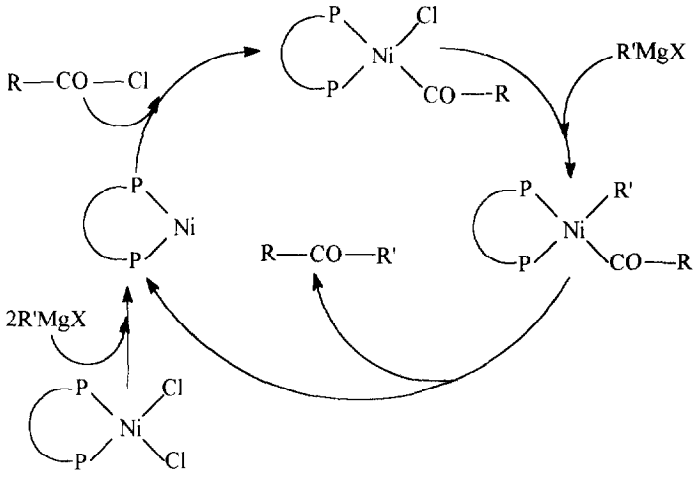
Table

Run	Substrate[a]	Nucleophile[b]	Product[c]	Rndt[d]
1	PhCOCl	EtMgBr	PhCOEt	70[e]
2	PhCOCl	EtMgBr	PhCOEt	56
3	PhCOCl	PhMgBr	PhCOPh	100
4	PhCOCl			92
5	PhCOCl	$nC_8H_{17}MgBr$	$PhCOC_8H_{17}$	91
6	PhCOCl	iBuMgBr	PhCOBu^i	89
7	PhCOCl			91
8	Ph-CH(CH$_3$)-CH$_2$-COCl	PhMgBr		100
9	Ph-CH(CH$_3$)-CH$_2$-COCl			100
10		PhMgBr		80[f][g]
11		PhMgBr		62[g]
12	Cl-CO-CO-Cl			80[h]
13	PhCOCl			20
14	PhCOCl			72

Notes: (a) the benzoyl chloride and the oxallyl chloride are commercially available, the other acyl halides were prepared by standard procedures from the acid with oxallyl chlorides in toluene; (b) the Grignard reagents were prepared in THF from the corresponding halides; (c) the structures of the products were in accordance with ^1H-, ^{13}C-NMR, GCMS and FTIR analyses; (d) on the purified products; (e) reaction carried out with addition of NaI (1 mol equivalent respect to the substrate) to the catalyst; (f) the by-products are traces of phenyl 2-decenyl ketone (5%); (g) by-products of THF ring opening by acyl halides are present; (h) the by-product is the 2,2-dithiophenyl ketone that can be easily eliminated by distillation.

The reaction seems to proceed via a nickel(II) carbonyl intermediate that undergoes a reductive elimination giving the target molecule (Scheme 2).

Scheme 2



In a typical run, a solution of $NidppeCl_2$ ($2 \cdot 10^{-5}$ mol) in THF (100 ml) and the suitable acyl bromide (0.01 mol) was reacted with a solution of the Grignard reagent (0.011 mol) in the same solvent at 0 °C. After the hydrolysis with a saturated NH_4Cl solution, the organic layers, extracted with diethyl ether and with hot hexane, gave the crude product in high chemical purity.

When aryl halides are employed the yield of the reaction can be increased using a stoichiometric amount of NaI in the solution before adding the Grignard reagent (Table, run 1,2); on the other hand, the use of NaI with acyl halides causes the formation of by-products due to the opening[9] of the THF ring.

To avoid double bond isomerization triphenylphosphine (10 molar equivalents with $NidppeCl_2$) must be added to the reaction mixture after adding the nucleophile (Table, run 10).

Furthermore, it must be underlined that the reaction can be employed successfully to prepare 1,2-diketones or 2-acyldithianes (Table, run 12-14) not directly obtainable with other metodologies[10].

Other studies are in progress to verify the applicability of this new sinthetic approach.

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