

A HIGHLY EFFICIENT SYNTHETIC ROUTE TO KETONES THROUGH SEQUENTIAL COUPLING
REACTIONS OF GRIGNARD REAGENTS WITH S-PHENYL CARBOCHLORIDOTHIOATE
IN THE PRESENCE OF NICKEL OR IRON CATALYSTS

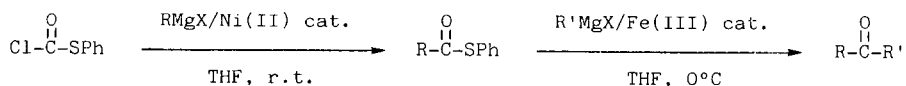
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Summary: The sequential coupling reactions of Grignard reagents with S-phenyl carbonochloridothioate in the presence of nickel(II) or iron(III) catalysts provides a very mild and straightforward route to symmetrical and unsymmetrical aliphatic and aromatic ketones.

It has been generally accepted that the synthesis of ketones by the Grignard reaction of carboxylic acid derivatives is usually unsatisfactory owing to the formation of undesired tertiary alcohols¹. At variance with this opinion we showed that ketones can be obtained even from carboxylic acids without significant amounts of alcohols provided that a suitable catalyst is used for the cross-coupling reactions². We obtained even more satisfactory results in an investigation in which acyl chlorides were reacted with Grignard reagents in the presence of tris(acetylacetonate)iron(III) at room temperature³. The latter procedure is quite general and, after our work, it has been already applied by other authors to the synthesis of 2,4,6-cycloheptatrienyl ketones⁴ and (S)-(-) and (R)-(+)-3-methoxy-3-phenyl-4,4,4-trifluoro-2-butanone⁵, which are not easily prepared by other known procedures^{5,6}.

As part of our continuing interest on the carbon-carbon bond formation by the use of transition metal catalyzed Grignard reactions⁷, we can now report an easy and efficient novel strategy for the synthesis of ketones based on two sequential cross-coupling reactions between the commercially available S-phenyl carbonochloridothioate and Grignard reagents in the presence of nickel(II) or iron(III) complexes as catalysts, according to the following equation:



The synthetic strategy outlined in the equation requires that, in the first step, selective substitution of the chlorine atom occurs without concomitant displacement of the phenylthio-group. We have achieved this goal by the use of two different catalysts in the two steps of the reaction. In fact, in the presence of catalytic amounts of dichloro [1,2-bis(diphenylphosphino)ethane]nickel(II), Ni(dppe)Cl₂, the coupling reaction of Grignard reagents with S-phenyl carbonochloridothioate occurs selectively at the carbon-chlorine bond to produce the corresponding S-phenyl carbothioates in high isolated yields (Table, step i). The S-phenyl carbothioate can then be reacted with several Grignard reagents in the presence of catalytic amounts of tris(acetylacetonate)iron(III), Fe(acac)₃, yielding various symmetrical (R=R') and unsymmetrical (R≠R') ketones in nearly quantitative yields (Table, step ii).

The reactions can be also carried out in one pot by adding, after completion of the first step, Fe(acac)₃ and the second Grignard reagent to the mixture containing the intermediate S-phenyl carbothioate without isolation of the latter (entries 6 and 11). However, the overall yields are generally lower.

As illustrated by the entries in the Table, the procedure provides a straightforward method for the synthesis of aliphatic and aromatic ketones, with the following features making it particularly attractive: i) all couplings proceed under mild conditions (0°C - r.t.); ii) both aromatic and aliphatic Grignard reagents can be used; iii) the reactions are clean and require a simple work-up for the isolation of the products; iv) the reaction times are short (5-10 min); v) the yields are high and in many cases nearly quantitative; vi) the first step of our procedure represents a versatile tool for the synthesis of carbothioate S-esters from commercially available materials, thus giving an interesting alternative to the other methods presently available for this useful class of compounds.⁸

Preparation of S-Phenyl Carbothioates. In a typical procedure: A 0.88 M freshly prepared solution of n-heptylmagnesium bromide in THF (10 ml, 8.8 mmol) was added dropwise, under nitrogen, to a stirred solution of freshly distilled S-phenyl carbonochloridothioate (1.38 g, 8 mmol) and Ni(dppe)Cl₂ (0.14 g, 0.26 mmol) in 60 ml of dry THF at room temperature. After complete addition, the stirring was continued for 5-10 min at the same temperature. Then, the reaction was quenched with aqueous HCl (10%) and extracted with several portions of ether. The combined ether extracts were washed with aqueous NaHCO₃ (5%), water, and dried over Na₂SO₄. The solvent was removed and the residue gave almost pure S-phenyl octanethioate (90%; GLC yield). The resulting crude product was distilled to give 1.6 g (85% yield) of pure S-phenyl octanethioate (b.p. 119-120°C/0.1 mmHg).

Preparation of Ketones. In a typical procedure: A 0.86 M freshly prepared solution of isopropylmagnesium chloride in THF (10 ml, 8.6 mmol) was added dropwise, under nitrogen, to a stirred solution of S-phenyl octanethioate (1.45 g, 6.1 mmol) and Fe(acac)₃ (0.09 g, 0.26 mmol) in

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Sequential cross-coupling reactions of S-phenyl carbonochloridothioate with Grignard reagents in the presence of Ni(dppe)Cl₂ or Fe(acac)₃ as catalysts.

$$\text{Cl}-\overset{\text{O}}{\parallel}{\text{C}}-\text{SPh} \xrightarrow[\text{THF, r.t.}]{\text{i, RMgX}^{\text{a}}/\text{Ni(dppe)Cl}_2} \text{R}-\overset{\text{O}}{\parallel}{\text{C}}-\text{SPh} \xrightarrow[\text{THF, 0}^\circ\text{C}]{\text{ii, R'MgX}^{\text{a}}/\text{Fe(acac)}_3} \text{R}-\overset{\text{O}}{\parallel}{\text{C}}-\text{R}'$$

Entry	Step i ^b			Step ii ^c		
	R	<u>S</u> -Phenyl carbothioate	Yield ^d %	R'	Ketone	Yield ^d %
1	<u>n</u> -C ₇ H ₁₅	<u>n</u> -C ₇ H ₁₅ -CO-SPh	90 (85)	<u>n</u> -C ₄ H ₉	<u>n</u> -C ₇ H ₁₅ -CO-C ₄ H ₉ - <u>n</u>	93 (88)
2				<u>i</u> -C ₃ H ₇	<u>n</u> -C ₇ H ₁₅ -CO-C ₃ H ₇ - <u>i</u>	99 (95)
3				<u>n</u> -C ₇ H ₁₅	<u>n</u> -C ₇ H ₁₅ -CO-C ₇ H ₁₅ - <u>n</u>	95
4	<u>n</u> -C ₅ H ₁₁	<u>n</u> -C ₅ H ₁₁ -CO-SPh	87 (79)	Ph	<u>n</u> -C ₅ H ₁₁ -CO-Ph	80
5				<u>n</u> -C ₅ H ₁₁	<u>n</u> -C ₅ H ₁₁ -CO-C ₅ H ₁₁ - <u>n</u>	87
6				<u>n</u> -C ₅ H ₁₁	<u>n</u> -C ₅ H ₁₁ -CO-C ₅ H ₁₁ - <u>n</u>	58 ^e
7	<u>i</u> -C ₃ H ₇ ^{f,g}	<u>i</u> -C ₃ H ₇ -CO-SPh	85 (78)	<u>n</u> -C ₇ H ₁₅	<u>i</u> -C ₃ H ₇ -CO-C ₇ H ₁₅ - <u>n</u>	98
8				Ph	<u>i</u> -C ₃ H ₇ -CO-Ph	85
9	Ph	Ph-CO-SPh	96 (87)	CH ₃ ^{g,h}	Ph-CO-CH ₃	80
10				<u>n</u> -C ₄ H ₉	Ph-CO-C ₄ H ₉ - <u>n</u>	94 (85)
11				<u>n</u> -C ₄ H ₉	Ph-CO-C ₄ H ₉ - <u>n</u>	65 ^e
12				<u>i</u> -C ₃ H ₇	Ph-CO-C ₃ H ₇ - <u>i</u>	95 (89)

a) Grignard reagents were prepared in THF from the corresponding bromides. b) All reactions were performed at room temperature on a 8 mmol scale with a reactant ratio S-phenyl carbonochloridothioate/RMgX/Ni(dppe)Cl₂ = 1/1.1/0.033. c) All reactions were performed at 0°C on a 6 mmol scale with a reactant ratio S-phenyl carbothioate/R'MgX/Fe(acac)₃ = 1/1.4/0.042. d) Yields determined by GLC analysis; yields of isolated purified products are given in parentheses. All reaction products were identified by comparison of their physical and spectral properties with those of authentic samples. e) Both steps were carried out in one pot without isolation of the intermediate S-phenyl carbothioate. f) Reaction at 0°C. g) Grignard reagent was prepared in THF from the corresponding chloride. h) Three equivalents of methylmagnesium chloride were used to ensure complete reaction.

60 ml of dry THF at 0°C. After complete addition, the stirring was continued for 5-10 min at the same temperature. Then, the reaction was quenched with aqueous HCl (10%) and extracted with several portions of ether. The combined ether extracts were washed with aqueous NaOH (10%), water, and dried over Na_2SO_4 . The solvent was removed and the residue gave almost pure 2-methyl-3-decanone (99%; GLC yield). The resulting crude product was distilled to give 1 g (95% yield) of 2-methyl-3-decanone (b.p. 78-79°C/ 4 mmHg).

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References and Notes

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