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One-step synthesis of 1,*n*-dicarbonyl compounds from carboxylic acid derivatives and di-Grignard reagents in the presence of transition metal catalysts

F. Babudri, A. D'Ettole, V. Fiandanese, G. Marchese * and F. Naso

Centro CNR di Studio sulle Metodologie Innovative di Sintesi Organiche, Dipartimento di Chimica, Università di Bari, via Amendola 173, 70126 Bari (Italy)

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Abstract

The transition metal catalyzed cross-coupling reaction of alkane di-Grignard reagents with carboxylic acid derivatives provides a convenient one-step synthesis of symmetrical 1,*n*-diketones ($n \geq 8$) and long-chain dicarboxylic thiol esters.

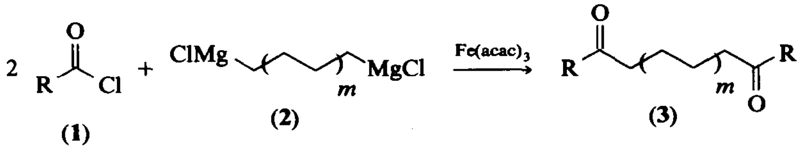
Introduction

We have previously shown that the synthesis of ketones by Grignard reaction of carboxylic acids [1] or acyl chlorides [2,3] can be carried out without concomitant formation of alcohols provided that a suitable catalyst is used for the cross-coupling reactions. We have also devised a more straightforward route for the synthesis of symmetric and unsymmetric 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 [4]. An extension of this methodology to Grignard reagents derived from β-halo ketals and acetals enabled us to devise a simple and short route to 1,4-diketones and 1,4-ketoaldehydes, which were utilized in an efficient synthesis of *Z*-jasmone and dihydrojasmone [5].

We now report a new one-step procedure for the synthesis of symmetrical 1,*n*-diketones ($n \geq 8$) and long-chain dicarboxylic thiol esters.

Results

The symmetrical 1,*n*-diketones were synthesized according to Eq. 1:

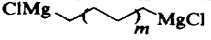
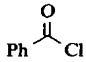
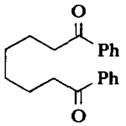
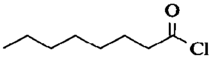
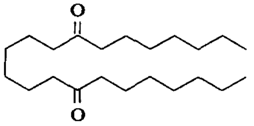
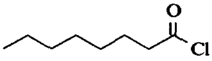
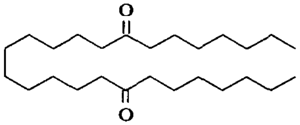
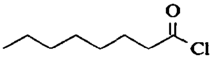
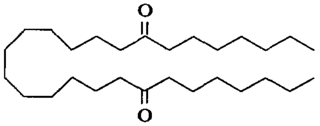
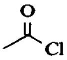
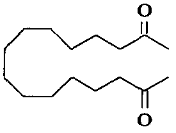
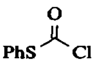
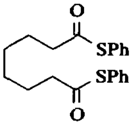
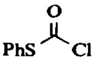
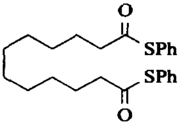
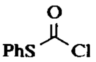
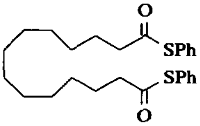


(1)

Thus the key to our synthetic approach is the successful utilization of di-Grignard reagents **2** in the catalyzed cross-coupling reaction with acyl chlorides **1**.

Table 1

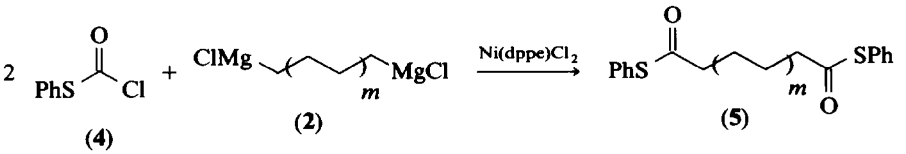
Synthesis of 1,*n*-diketones **3a–e** and dicarboxylic thiol esters **5a–c**

Entry	Substrate		Product	No.	Yield [a] (%)
1		$m = 2$		**3a**	65
2		$m = 2$		**3b**	72
3		$m = 4$		**3c**	70
4		$m = 5$		**3d**	71
5		$m = 5$		**3e**	80
6		$m = 2$		**5a**	78
7		$m = 4$		**5b**	80
8		$m = 5$		**5c**	73

[a] Isolated yields based on amounts of di-Grignard reagents taken.

The standard preparation of di-Grignard reagents **2** involves the reaction of the corresponding alkyl dibromides or dichlorides with magnesium in THF or diethyl ether [6]. We carried out some preliminary studies aimed at determining suitable experimental conditions for the conversion of such dihalides to di-Grignard reagents to be used in the coupling reactions. It was found that the most satisfactory reagents for use in our cross-coupling procedure are THF solutions of the di-(chloromagnesio)alkanes, similar solutions of di(bromomagnesio) alkanes giving unsatisfactory results. As illustrated by the entries 1–5 in Table 1, the procedure works well with both aliphatic and aromatic acyl chlorides, and can be used successfully for the synthesis of various symmetrical 1,*n*-diketones **3a–e**, with isolated yields in the range 65–80% [7*]. The examples reported include the one-step synthesis in 80% yield of the 2,15-hexadecanedione (**3e**), the well known precursor of muscone [8], a naturally occurring compound with the odour of musk.

An additional illustration of the value of our procedure is provided by the synthesis, in good yields, of long-chain aliphatic dicarboxylic thiol esters **5** (Eq. 2) from commercially available (*S*-phenylthio)carbonyl chloride **4**.



(2)

It is important to note that in this case the selective substitution of the chlorine atom, without concomitant displacement of the phenylthio group, can be successfully carried out by using dichloro[1,2-bis(diphenylphosphino)ethane]nickel(II) as a catalyst [4]. Some representative examples are given in Table 1 (entries 6–8).

The approach described here should provide an efficient one-step procedure for the synthesis of 1,*n*-dicarbonyl compounds, which are important in the construction of many-membered carbocycles [9] and heterocyclic compounds [10]. Moreover, taking into account the ready availability of the starting materials, the simplicity of the operations involved, and the good yields, we believe that our method compares favourably with the available alternatives [11].

Experimental

All reactions and transfers involving organometallic compounds were carried out under nitrogen. Tetrahydrofuran (THF) was dried by refluxing the commercial solvent with sodium/benzophenone and distilled, prior to use, under nitrogen. (*S*-Phenylthio)carbonyl chloride, acyl chlorides, $NiCl_2(dppe)$, and $Fe(acac)_3$ were commercial samples. The dichloroalkanes used in this work were also commercial products, except for 1,12-dichlorododecane, which was prepared from 1,12-dodecanediol by a known procedure [12]. ^1H NMR spectra were recorded in deuteriochloroform ($CDCl_3$) on a Varian XL-200, 200 MHz, spectrometer. GLC/Mass-spectrometry analyses were performed with a Hewlett-Packard 5890A gas chromatograph equipped with a fused silica capillary column SE 30, 30 m, and a Hewlett-Packard Mass Selective Detector MSD 5970B. Elemental analyses were performed on a Carlo Erba-Instruments 1106 analyser. Melting points are uncorrected.

Grignard reagents

All the di-Grignard reagents were prepared immediately before use as follows. In a 100 ml round-bottomed flask equipped with magnetic stirrer, condenser and addition funnel, magnesium turnings (2.88 g, 0.12 mol) were flame dried under a

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* Reference number with asterisk indicates a note in the list of references.

nitrogen stream and then allowed to cool to room temperature. Anhydrous THF (10 ml) was introduced and 1,2-dibromoethane (0.5 ml) then added in one portion. An exothermic reaction began and the solvent started to reflux. A solution of dichloroalkane (30 mmol) in THF (50 ml) was then added dropwise during 4 h with stirring, the temperature of the reaction mixture being kept at 60 °C with a warm water bath. After the addition the mixture was stirred at 60 °C for 1 h, then cooled to room temperature and filtered under nitrogen through a sintered glass disc into a dry storage container. The concentration of the di-Grignard solution was determined by the standard acidimetric procedure [13]. Yields were commonly in the range 87–95%.

Coupling reactions

(a) 1,n-Diketones 3a–e. A solution of 1,*n*-di(chloromagnesio)alkane in THF (10 mmol) was added dropwise at 0 °C and under nitrogen to a stirred solution of freshly distilled acyl chloride (26 mmol) and tris(acetylacetonate)iron(III), ($Fe(acac)_3$), (0.21 g, 0.60 mmol) in 40 ml of anhydrous THF. The mixture was then warmed to room temperature, stirred for an additional 1 h, then treated with aqueous NH_4Cl. The organic material was extracted with chloroform and the extract washed with water and dried over anhydrous Na_2SO_4. The solvent was removed in vacuo and the crude products **3a–e** were purified by recrystallization from ethanol or ethyl ether.

2,15-Hexadecanedione (**3e**) was identified from available spectral and physical data [8a,b]. Elemental and spectral data (MS and ^1H NMR) of the other coupling products are given below.

1,8-Diphenyl-1,8-octanedione (**3a**). M.p. 89–90 °C (ethanol), lit. [14]: 91 °C. Anal. Found: C, 81.82; H, 7.66. $C_{20}H_{22}O_2$ calcd.: C, 81.60; H, 7.53%. ^1H NMR (δ ppm): 1.38–1.52 (m, 4H), 1.68–1.84 (m, 4H), 2.97 (t, J 7.3 Hz, 4H), 7.40–7.65 (m, 6H), and 7.80–8.00 (m, 4H). MS (70 eV) m/z (%): 276 (10), 252 (5), 175 (19), 120 (33), 105 (100), 77 (45), 51 (9).

8,15-Docosanedione (**3b**). M.p. 87–88 °C (ethanol). Anal. Found: C, 77.91; H, 12.77. $C_{22}H_{42}O_2$ calcd.: C, 78.04; H, 12.50%. ^1H NMR (δ ppm): 0.78–0.94 (br. t, 6H), 1.24 (br. s, 20H), 1.44–1.64 (m, 8H), and 2.36 (t, J 7.3 Hz, 8H). MS (70 eV) m/z (%): 338 (M^+, 1), 254 (6), 239 (9), 198 (6), 197 (42), 155 (10), 152 (10), 142 (43), 127 (63), 109 (14), 57 (100), 43 (47), 41 (39).

8,19-Hexacosanedione (**3c**). M.p. 91–93 °C (ethyl ether). Anal. Found: C, 79.05; H, 12.98. $C_{26}H_{50}O_2$ calcd.: C, 79.12; H, 12.77%. ^1H NMR (δ ppm): 0.79–0.92 (br. t, 6H), 1.24 (br. s, 28H), 1.42–1.64 (m, 8H), and 2.36 (t, J 7.3 Hz, 8H). MS (70 eV) m/z (%): 394 (M^+, 1), 323 (5), 310 (6), 295 (6), 253 (27), 226 (24), 155 (10), 142 (34), 127 (58), 109 (13), 97 (12), 95 (12), 83 (16), 81 (10), 71 (19), 69 (16), 57 (100), 55 (36), 43 (48), 41 (33).

8,21-Octacosanedione (**3d**). M.p. 96–97 °C (ethanol). Anal. Found: C, 79.38; H, 13.10. $C_{28}H_{54}O_2$ calcd.: C, 79.55; H, 12.88%. ^1H NMR (δ ppm): 0.82–0.92 (br. t, 6H), 1.24 (br. s, 32H), 1.45–1.70 (m, 8H), and 2.37 (t, J 7.6 Hz, 8H). MS (70 eV) m/z (%): 422 (M^+, 1), 338 (5), 323 (6), 281 (26), 254 (20), 155 (10), 142 (32), 127 (52), 109 (11), 97 (15), 57 (100), 43 (43).

(b) Dicarboxylic thiol esters 5a–c. A solution of 1,*n*-di(chloromagnesio)alkane in THF (10 mmol) was added dropwise, under nitrogen, to a stirred solution of freshly distilled (*S*-phenylthio)carbonyl chloride (4.5 g, 26 mmol) and dichloro[1,2-bis(di-

phenylphosphino)ethane]nickel(II), $NiCl_2(dppe)$, (0.32 g, 0.60 mmol) in 40 ml of dry THF at 0 °C. Stirring was continued for 1 h at the same temperature. Aqueous NH_4Cl was added and the organic material extracted with several portions of chloroform. The combined extracts were washed with water, dried over anhydrous Na_2SO_4, and evaporated under reduced pressure. Flash chromatography of the residue on a silica gel column, with light petroleum/ether (90/10) as eluent, afforded **5a–c**, which were recrystallized from light petroleum to give analytical samples.

Details of significant ^1H NMR and mass spectral data are reported below, together with elemental analyses.

Octanebis(thioic)acid *S,S*-diphenyl ester (**5a**). M.p. 63–64 °C (light petroleum). Anal. Found: C, 67.00; H, 6.33; S, 17.76. $C_{20}H_{22}O_2S_2$ calcd.: C, 67.00; H, 6.18; S, 17.89%. ^1H NMR (δ ppm): 1.30–1.57 (m, 4H), 1.65–1.85 (m, 4H), 2.66 (t, J 7.4 Hz, 4H), and 7.41 (s, 10H). MS (70 eV) m/z (%): 249 (34), 139 (89), 137 (11), 121 (13), 111 (20), 110 (22), 109 (84), 83 (34), 77 (11), 69 (25), 55 (100), 41 (46).

Dodecanebis(thioic)acid *S,S*-diphenyl ester (**5b**). M.p. 74–75 °C (light petroleum). Anal. Found: C, 69.77; H, 7.33; S, 15.37. $C_{24}H_{30}O_2S_2$ calcd.: C, 69.52; H, 7.29; S, 15.47%. ^1H NMR (δ ppm): 1.29 (br. s, 12H), 1.60–1.80 (m, 4H), 2.65 (t, J 7.5 Hz, 4H), and 7.40 (s, 10H). MS (70 eV) m/z (%): 305 (41), 195 (29), 167 (4), 149 (20), 111 (17), 110 (26), 109 (54), 97 (18), 83 (38), 69 (47), 57 (13), 55 (100), 43 (33), 41 (57).

Tetradecanebis(thioic)acid *S,S*-diphenyl ester (**5c**). M.p. 70–71 °C (light petroleum). Anal. Found: C, 70.66; H, 7.96; S, 14.42. $C_{26}H_{34}O_2S_2$ calcd.: C, 70.54; H, 7.74; S, 14.49%. ^1H NMR (δ ppm): 1.28 (br. s, 16H), 1.60–1.85 (m, 4H), 2.66 (t, J 7.4 Hz, 4H), and 7.41 (s, 10H). MS (70 eV) m/z (%): 333 (34), 223 (22), 195 (4), 135 (8), 121 (12), 110 (25), 109 (49), 97 (21), 83 (26), 69 (48), 55 (100), 43 (38), 41 (50).

Acknowledgements

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