

# Reduction of 2,2,2-trichloro-1-arylethanones by RMgX: mechanistic investigation and the synthesis of substituted $\alpha,\alpha$ -dichloroketones†

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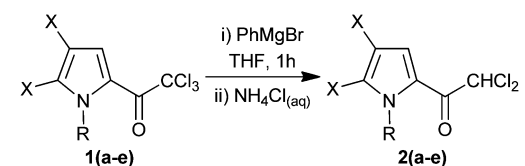
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**2,2,2-Trichloro-1-arylethanones undergo high yielding reductions to the corresponding 2,2-dichloro-1-arylethanones in the presence of RMgX. A single electron transfer mechanism for the reaction is proposed based on trapping experiments. Reaction of the intermediate enolates with a range of electrophiles is described, providing a convenient route to substituted  $\alpha,\alpha$ -dichloro- $\beta$ -hydroxyketones and related molecules.**

$\alpha,\alpha$ -Dichlorocarbonyls are versatile synthetic intermediates, typically formed by  $\alpha$ -chlorination of carbonyls,<sup>1</sup> chlorination of silyl enolates,<sup>2</sup> electrochemical or metal mediated reductions,<sup>3</sup> aldol reactions<sup>4</sup> or cycloadditions with dichloroketene.<sup>5</sup>  $\alpha,\alpha$ -Dichlorocarbonyl groups have been employed in intramolecular radical cyclisations,<sup>6</sup> have been converted to chloroalkenes,<sup>7</sup> chlorooxiranes allowing access to  $\alpha$ -keto esters<sup>8</sup> and heteroaromatics,<sup>9</sup> have been used as chlorinating agents<sup>10</sup> and were found in the natural product chlorotonil A.<sup>11</sup> In designing new routes to functionalised  $\alpha,\alpha$ -dichlorocarbonyls, we decided to investigate conditions for the reduction of 2,2,2-trichloro-1-arylethanones. We envisaged that 2,2,2-trichloro-1-arylethanones being sterically hindered and electron-deficient aromatic ketones, would form reactive ketyl radical anions in the presence of a suitable single electron donor such as a Grignard reagent.<sup>12</sup> Further reaction of the intermediate ketyl radical anion would then provide a new route towards substituted  $\alpha,\alpha$ -dichloroketones.

Our initial investigations involved the addition of commercially available 2,2,2-trichloro-1-(1*H*-pyrrol-2-yl)ethanone (**1a**) to PhMgBr, followed by quenching with excess aqueous  $\text{NH}_4\text{Cl}$ .

**Table 1** Reaction of PhMgBr with substituted 2,2,2-trichloro-1-(1*H*-pyrrol-2-yl)ethanones<sup>a</sup>



Entry	R	X	PhMgBr	Temp.	Product	Yield <sup>b</sup> (%)
1	H	H	1.1 eq.	0 °C	<b>2a</b>	50
2	H	H	1.1 eq.	r.t.	<b>2a</b>	55
3	H	H	2.2 eq.	r.t.	<b>2a</b>	90
4	Me	H	1.0 eq.	r.t.	<b>2b</b>	94
5	H	Cl	2.0 eq.	r.t.	<b>2c</b>	87
6	H	Br	2.0 eq.	r.t.	<b>2d</b>	95
7	H	I	2.0 eq.	r.t.	<b>2e</b>	93

<sup>a</sup> The reactions were performed by reverse addition of 1 mmol of ketone in 1 mL of THF to a 2 M solution of PhMgBr in THF. <sup>b</sup> Isolated yields.

With the use of 1.1 equivalents of PhMgBr, at either 0 °C or r.t., the reaction resulted in the isolation of 2,2-dichloro-1-(1*H*-pyrrol-2-yl)ethanone (**2a**) in 50–55% yield (Table 1, entries 1 and 2), formally a C–Cl to C–H reduction.

We postulated that the reaction may not go to completion due to competing deprotonation of the pyrrolic NH. Thus we re-examined the reaction of compound **1a** with 2.2 equivalents PhMgBr at r.t., and the reaction of compound **1b** (an analogous *N*-methylated compound) with 1.0 equivalents of PhMgBr (Table 1, entries 3 and 4). In both cases near-quantitative yields of the corresponding reduced compounds **2a** and **2b** were isolated after quenching of the reaction. In addition three di-halogenated pyrrole derivatives (**1c–e**) were also submitted to the optimised reaction conditions, again yielding the corresponding reduced products (**2c–e**) in high yield. Observation of this C–Cl to C–H reduction prompted us to investigate the mechanism in more detail.

After the reaction of **1a–e** with PhMgBr and quenching with aqueous  $\text{NH}_4\text{Cl}$ , a major by-product was observed by <sup>1</sup>H NMR spectroscopy of the crude reaction mixtures, which on isolation by silica gel chromatography was identified as 1,1'-biphenyl.

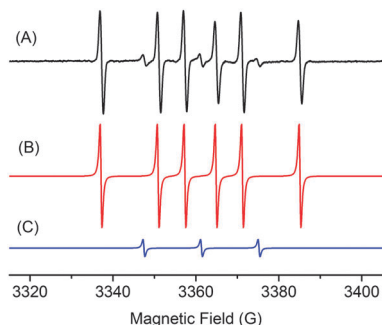
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† Electronic supplementary information (ESI) available: Experimental procedures, <sup>1</sup>H and <sup>13</sup>C spectra and X-ray structures. Crystallographic data for **1d**, **3a**, **3b**, **3f**, **3g** and **3h**, have been deposited with the CCDC, deposition nos: CCDC 916095–916100. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/c3cc39147g



**Fig. 1** (A) X-band EPR spectrum at 270 K of a THF solution resulting from the reaction of PhMgBr with ketone **1b**, in the presence of DMPO; (B) simulated spectrum of the Ph-DMPO adduct with the parameters:  $g = 2.0096$ ;  $a(^1\text{H}) = 20.3$  G and  $a(^{14}\text{N}) = 13.87$  G; (C) simulated spectrum of the Ph<sub>2</sub>-DMPO adduct, with  $g = 2.0095$  and  $a(^{14}\text{N}) = 13.87$  G. (100 kHz modulation frequency, 1 G modulation amplitude, 0.27 mW incident microwave power).

In the case of entry 3, 40 mg of 1,1'-biphenyl could be isolated, corresponding to approximately 50% of the total added PhMgBr. The formation of significant quantities of 1,1'-biphenyl is most likely to arise from the dimerisation of phenyl radicals generated during the reaction.<sup>13,14</sup>

To examine this supposition further we carried out an *in situ* EPR experiment. Solutions containing ketone **1b** and PhMgBr in THF were added sequentially to an EPR tube cooled in liquid N<sub>2</sub>. Further addition of the spin trap 5,5-dimethyl-1-pyrroline *N*-oxide (DMPO) and subsequent warming to 270 K of the reaction mixture produced a species with a well-resolved, 6-line EPR spectrum (Fig. 1), corresponding to a Ph-DMPO adduct (2,2-dimethyl-5-phenylpyrrolidin-1-olate radical) with distinctive <sup>1</sup>H and <sup>14</sup>N hyperfine coupling constants:  $a(^1\text{H}) = 20.3$  G and  $a(^{14}\text{N}) = 13.87$  G. A minor product, the 2,2-dimethyl-5,5-diphenylpyrrolidin-1-olate radical, was also observed in the EPR spectrum (3 lines,  $a(^{14}\text{N}) = 13.87$  G). In the absence of ketone **1b** neither adduct was observed, indicating that the Ph radical is generated under the reaction conditions.

To further probe 1,1'-biphenyl formation we examined the reaction between ketone **1b** and a number of other RMgX species, where R was a *para*-substituted phenyl group (Table 2).

Reaction of 4-Me(C<sub>6</sub>H<sub>4</sub>)MgI with ketone **1b** (Table 2, entry 1) gave 4,4'-dimethyl-1,1'-biphenyl as a single regioisomer. One to one mixtures of *para*-substituted phenyl Grignard reagents (Table 2, entries 2–4) gave in each case a mixture of 4,4'-disubstituted-1,1'-biphenyl products. This suggests that the aryl-aryl bond is being formed at the position of the original C–Mg bond, supporting the formation 1,1'-biphenyl products *via* a radical coupling mechanism. This suggests that the RMgX is donating a single electron from the R–Mg bond to the substrate.

We postulated that the overall reaction involves a late stage enolate intermediate, which is quenched by aqueous NH<sub>4</sub>Cl to give the observed reduction product. To confirm this, ketones **1b**, **1f** and **1g** were reacted with PhMgBr and quenched with D<sub>2</sub>O to give, in 50–96% yield, the corresponding deuterated products **2b**, **2f**, and **2g** with high levels of D incorporation (Table 3).

We then investigated the influence of the R (aryl, alkyl) and X (halogen) groups of the Grignard reagent (Table 4).

**Table 2** Reaction of RMgX/R'MgX with ketone **1b**

i) 0.5 eq. RMgX 0.5 eq. R'MgX THF, r.t., 1h <b>1b</b> $\xrightarrow{\text{ii) NH}_4\text{Cl(aq)}}$ <b>2b</b> + R–R + R–R' + R'–R'					
Entry	RMgX	R'MgX	Yields <sup>a</sup> (%)		
			R–R	R–R'	R'–R'
1	4-Me(C <sub>6</sub> H <sub>4</sub> )MgI	4-Me(C <sub>6</sub> H <sub>4</sub> )MgI	66	—	—
2	4-Me(C <sub>6</sub> H <sub>4</sub> )MgI	PhMgI	14 <sup>b</sup>	24 <sup>b</sup>	23
3	4-MeO(C <sub>6</sub> H <sub>4</sub> )MgI	4-Me(C <sub>6</sub> H <sub>4</sub> )MgI	43	0	16
4	4-MeO(C <sub>6</sub> H <sub>4</sub> )MgBr	PhMgBr	0	43	20

<sup>a</sup> Isolated yields. <sup>b</sup> Products not separable, yield determined by GC-MS.

**Table 3** Reaction trapping with D<sub>2</sub>O

$\text{Ar-C(=O)-CCl}_3 \xrightarrow[\text{ii) D}_2\text{O}]{\text{i) 1.1 eq. PhMgBr, THF, r.t., 1h}} \text{Ar-C(=O)-CDCl}_2$			
<b>1(b,f,g)</b>	<b>2(b,f,g)</b>		
Ar	Product	Yield of <b>2</b> <sup>a</sup> (%)	% D <sup>b</sup>
1-Methyl-1 <i>H</i> -pyrrol-2-yl	(2- <i>d</i> )- <b>2b</b>	86	89
<i>p</i> -Tolyl	(2- <i>d</i> )- <b>2f</b>	50	>95
1-(4-( <i>tert</i> -Butyl)phenyl)	(2- <i>d</i> )- <b>2g</b>	96	93

<sup>a</sup> Isolated yields. <sup>b</sup> % Deuterium incorporation estimated by <sup>1</sup>H NMR.

**Table 4** Influence of R and X substituents

$\text{Ar-C(=O)-CCl}_3 \xrightarrow[\text{ii) NH}_4\text{Cl(aq)}]{\text{i) 1 eq. RMgX, THF, r.t., 1h}} \text{Ar-C(=O)-CHCl}_2 + \text{R-R}$					
<b>1(b,f,g)</b>	<b>2(b,f,g)</b>				
Entry	R	X	Ar	Yield/ <b>2</b> <sup>a</sup> (%)	Yield/R <sub>2</sub> <sup>b</sup> (%)
1	Et	Br	1-Methyl-1 <i>H</i> -pyrrol-2-yl ( <b>1b</b> )	50	nd
2	i-Pr	Cl	1-Methyl-1 <i>H</i> -pyrrol-2-yl ( <b>1b</b> )	42	nd
3	Ph	Cl	1-Methyl-1 <i>H</i> -pyrrol-2-yl ( <b>1b</b> )	61	45
4	Ph	Br	1-Methyl-1 <i>H</i> -pyrrol-2-yl ( <b>1b</b> )	94	52
5	Ph	I	1-Methyl-1 <i>H</i> -pyrrol-2-yl ( <b>1b</b> )	94	62
6	Et	Br	<i>p</i> -Tolyl ( <b>1f</b> )	33	nd
7	i-Pr	Cl	<i>p</i> -Tolyl ( <b>1f</b> )	33	nd
8	Ph	Cl	<i>p</i> -Tolyl ( <b>1f</b> )	47	35
9	Ph	Br	<i>p</i> -Tolyl ( <b>1f</b> )	68	38
10	Ph	I	<i>p</i> -Tolyl ( <b>1f</b> )	96	71
11	Ph	Br	1-(4-( <i>tert</i> -Butyl)phenyl) ( <b>1g</b> )	71	39
12	Ph	I	1-(4-( <i>tert</i> -Butyl)phenyl) ( <b>1g</b> )	98	58

<sup>a</sup> Isolated yields. <sup>b</sup> Yield based on total RMgX added.

A comparison of Et, i-Pr and Ph groups (Table 4) showed that the highest yields resulted from the use of aryl Grignards.<sup>15</sup> In addition, reaction yields showed the trend: X = I > Br > Cl.

Variation of solvent (THF, Et<sub>2</sub>O and hexane) and concentration had little effect on reaction outcomes. Only with extreme dilution was any influence noticeable (see ESI†).

Therefore we propose a potential mechanism for the Grignard-mediated reduction of trichloroacetyl-substituted aromatics. We suggest that the first step of the reaction is a single electron transfer from the Grignard reagent to the ketone. This intermediate radical anion then either: (a) loses

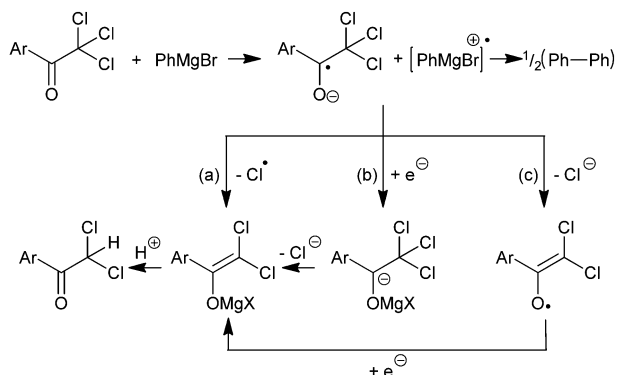


Fig. 2 Proposed reaction pathways.

Table 5 RMgX mediated reduction/functionalisation of 2,2,2-trichloro-1-(1-methyl-1H-pyrrol-2-yl)ethanone



Product <sup>a</sup>	Electrophile	R	Yield <sup>b</sup> (%)
3a	PhCHO	PhCH(OH)	81 <sup>c</sup>
3b	4-MeO(C <sub>6</sub> H <sub>4</sub> )CHO	4-MeO(C <sub>6</sub> H <sub>4</sub> )CH(OH)	85 <sup>c</sup>
3c	4-I(C <sub>6</sub> H <sub>4</sub> )CHO	4-I(C <sub>6</sub> H <sub>4</sub> )CH(OH)	94
3d	5-Me(C <sub>4</sub> H <sub>2</sub> O)CHO	5-Me(C <sub>4</sub> H <sub>2</sub> O)CH(OH)	70
3e	C <sub>6</sub> F <sub>5</sub> CHO	C <sub>6</sub> F <sub>5</sub> CH(OH)	70
3f	4-NO <sub>2</sub> (C <sub>6</sub> H <sub>4</sub> )CHO	4-NO <sub>2</sub> (C <sub>6</sub> H <sub>4</sub> )CH(OH)	96 <sup>c</sup>
3g	4-NO <sub>2</sub> (C <sub>6</sub> H <sub>4</sub> )CH <sub>2</sub> Cl	4-NO <sub>2</sub> (C <sub>6</sub> H <sub>4</sub> )CH <sub>2</sub>	37 <sup>c</sup>
3h	4-NO <sub>2</sub> (C <sub>6</sub> H <sub>4</sub> )COCl	4-NO <sub>2</sub> (C <sub>6</sub> H <sub>4</sub> )C(O)	95 <sup>c</sup>
3i	(EtO <sub>2</sub> C) <sub>2</sub> CO	(EtO <sub>2</sub> C) <sub>2</sub> C(OH)	75
3j	C <sub>6</sub> H <sub>5</sub> COCl	C <sub>6</sub> H <sub>5</sub> C(O)	50

<sup>a</sup> **1b** was reacted in THF with PhMgBr at r.t. for 1 h, after which a suitable electrophile was added and the mixture stirred at r.t. until TLC analysis showed that the reaction was complete. <sup>b</sup> Isolated yields. <sup>c</sup> Structures confirmed by single-crystal X-ray analysis.

a chlorine atom, (b) accepts a second electron and subsequently loses chloride or (c) loses chloride followed by addition of a second electron, to give the corresponding magnesium enolate (Fig. 2).<sup>16</sup>

Since the intermediate magnesium enolates can be intercepted by electrophiles, we have exploited this chemistry as a convenient "one-pot" reductive-functionalisation of 2,2,2-trichloro-1-(1-methyl-1H-pyrrol-2-yl)ethanone (**1b**) to give substituted  $\alpha,\alpha$ -dichloroketones. Reaction with 1-(chloromethyl)-4-nitrobenzene gave only a moderate yield of the expected product. Good yields were however obtained on reaction with diethyl 2-oxomalonate, aryl acid chlorides or aryl aldehydes (Table 5).<sup>17</sup>

In conclusion we have demonstrated a new approach to functionalised  $\alpha,\alpha$ -dichloroketones, *via* the reaction of commercially available RMgX reagents with 2,2,2-trichloro-1-arylethanones. Additional examination of the substrate scope and

investigations into subsequent synthetic modification of the  $\alpha,\alpha$ -dichloroketones formed will be discussed in future publications.

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- 13 Trace 2-phenyltetrahydrofuran could also be detected by <sup>1</sup>H NMR and GCMS, when reactions were carried out in THF. We postulate that this is formed through radical H abstraction from the  $\alpha$ -position of THF, followed by coupling of resulting THF derived radical with a phenyl radical.
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- 16 No evidence of atomic chlorine or bromine was observed by EPR. Neither C<sub>6</sub>H<sub>5</sub>Cl nor C<sub>6</sub>H<sub>5</sub>Br (the coupling products of phenyl radical and atomic halogen) could be detected by GCMS of the crude reaction mixture leading to **2b**.
- 17 The corresponding magnesium enolate can be prepared from **2b** through deprotonation with NaH in THF, followed by ion exchange with MgCl<sub>2</sub>. The enolate was reacted with D<sub>2</sub>O to give a 78% yield (84% deuterium incorporation by <sup>1</sup>H NMR) of (2-*d*)-**2b** or 4-NO<sub>2</sub>(C<sub>6</sub>H<sub>4</sub>)CHO to give a 47% yield of **3f**.