

Reduction of 2,2,2-trichloro-1-arylethanones by RMgX: mechanistic investigation and the synthesis of substituted α,α -dichloroketones†

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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 α,α -dichloro- β -hydroxyketones and related molecules.

α,α -Dichlorocarbonyls are versatile synthetic intermediates, typically formed by α -chlorination of carbonyls,¹ chlorination of silyl enolates,² electrochemical or metal mediated reductions,³ aldol reactions⁴ or cycloadditions with dichloroketene.⁵ α,α -Dichlorocarbonyl groups have been employed in intramolecular radical cyclisations,⁶ have been converted to chloroalkenes,⁷ chlorooxiranes allowing access to α -keto esters⁸ and heteroaromatics,⁹ have been used as chlorinating agents¹⁰ and were found in the natural product chlorotonil A.¹¹ In designing new routes to functionalised α,α -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.¹² Further reaction of the intermediate ketyl radical anion would then provide a new route towards substituted α,α -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 NH₄Cl.

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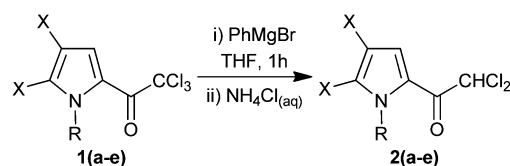
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† Electronic supplementary information (ESI) available: Experimental procedures, ¹H and ¹³C spectra and X-ray structures. Crystallographic data for **1d**, **3a**, **3b**, **3f**, **3g** and **3h**, have been deposited with the CCDC, deposition nos: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

Table 1 Reaction of PhMgBr with substituted 2,2,2-trichloro-1-(1*H*-pyrrol-2-yl)ethanones^a



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

^a 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. ^b 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 NH₄Cl, a major by-product was observed by ¹H NMR spectroscopy of the crude reaction mixtures, which on isolation by silica gel chromatography was identified as 1,1'-biphenyl.

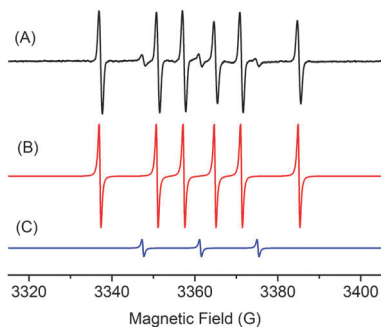


Fig. 1 (A) X-band EPR spectrum at 270 K of a THF solution resulting from the reaction of PhMgBr with ketone **1b**, in the presence of DMPO; (B) simulated spectrum of the Ph-DMPO adduct with the parameters: $g = 2.0096$; $a(^1\text{H}) = 20.3$ G and $a(^{14}\text{N}) = 13.87$ G; (C) simulated spectrum of the Ph₂-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.^{13,14}

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 N₂. 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 ¹H and ¹⁴N 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(C₆H₄)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 NH₄Cl to give the observed reduction product. To confirm this, ketones **1b**, **1f** and **1g** were reacted with PhMgBr and quenched with D₂O 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**

$$\text{1b} \xrightarrow[\text{ii) NH}_4\text{Cl(aq)}]{\text{i) 0.5 eq. RMgX, 0.5 eq. R'MgX, THF, r.t., 1h}} \text{2b} + \text{R-R} + \text{R-R}' + \text{R}'\text{-R}'$$

| Entry | RMgX | R'MgX | Yields ^a (%) | | |
|-------|---|---|-------------------------|-----------------|-------|
| | | | R-R | R-R' | R'-R' |
| 1 | 4-Me(C ₆ H ₄)MgI | 4-Me(C ₆ H ₄)MgI | 66 | — | — |
| 2 | 4-Me(C ₆ H ₄)MgI | PhMgI | 14 ^b | 24 ^b | 23 |
| 3 | 4-MeO(C ₆ H ₄)MgI | 4-Me(C ₆ H ₄)MgI | 43 | 0 | 16 |
| 4 | 4-MeO(C ₆ H ₄)MgBr | PhMgBr | 0 | 43 | 20 |

^a Isolated yields. ^b Products not separable, yield determined by GC-MS.

Table 3 Reaction trapping with D₂O

$$\text{Ar-C(=O)-CCl}_3 \xrightarrow[\text{ii) D}_2\text{O}]{\text{i) 1.1 eq. PhMgBr, THF, r.t., 1h}} \text{Ar-C(=O)-CDCl}_2$$

| Ar | Product | Yield of 2 ^a (%) | % D ^b |
|-----------------------------------|---------------------------|-----------------------------|------------------|
| 1-Methyl-1 <i>H</i> -pyrrol-2-yl | (2- <i>d</i>)- 2b | 86 | 89 |
| <i>p</i> -Tolyl | (2- <i>d</i>)- 2f | 50 | >95 |
| 1-(4-(<i>tert</i> -Butyl)phenyl) | (2- <i>d</i>)- 2g | 96 | 93 |

^a Isolated yields. ^b % Deuterium incorporation estimated by ¹H NMR.

Table 4 Influence of R and X substituents

$$\text{Ar-C(=O)-CCl}_3 \xrightarrow[\text{ii) NH}_4\text{Cl(aq)}]{\text{i) 1 eq. RMgX, THF, r.t., 1h}} \text{Ar-C(=O)-CHCl}_2 + \text{R-R}$$

| Entry | R | X | Ar | Yield/2 ^a (%) | Yield/R ₂ ^b (%) |
|-------|--------------|----|---|--------------------------|---------------------------------------|
| 1 | Et | Br | 1-Methyl-1 <i>H</i> -pyrrol-2-yl (1b) | 50 | nd |
| 2 | <i>i</i> -Pr | Cl | 1-Methyl-1 <i>H</i> -pyrrol-2-yl (1b) | 42 | nd |
| 3 | Ph | Cl | 1-Methyl-1 <i>H</i> -pyrrol-2-yl (1b) | 61 | 45 |
| 4 | Ph | Br | 1-Methyl-1 <i>H</i> -pyrrol-2-yl (1b) | 94 | 52 |
| 5 | Ph | I | 1-Methyl-1 <i>H</i> -pyrrol-2-yl (1b) | 94 | 62 |
| 6 | Et | Br | <i>p</i> -Tolyl (1f) | 33 | nd |
| 7 | <i>i</i> -Pr | Cl | <i>p</i> -Tolyl (1f) | 33 | nd |
| 8 | Ph | Cl | <i>p</i> -Tolyl (1f) | 47 | 35 |
| 9 | Ph | Br | <i>p</i> -Tolyl (1f) | 68 | 38 |
| 10 | Ph | I | <i>p</i> -Tolyl (1f) | 96 | 71 |
| 11 | Ph | Br | 1-(4-(<i>tert</i> -Butyl)phenyl) (1g) | 71 | 39 |
| 12 | Ph | I | 1-(4-(<i>tert</i> -Butyl)phenyl) (1g) | 98 | 58 |

^a Isolated yields. ^b 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.¹⁵ In addition, reaction yields showed the trend: X = I > Br > Cl.

Variation of solvent (THF, Et₂O 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

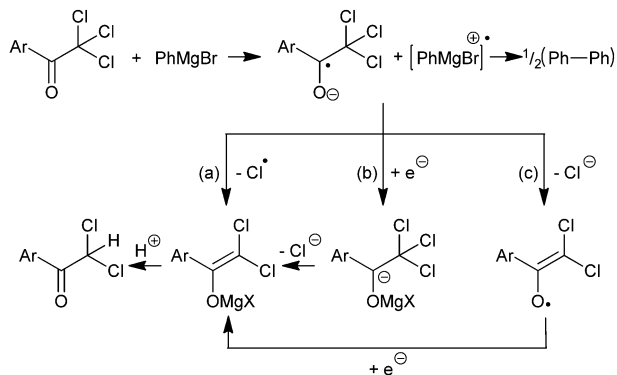
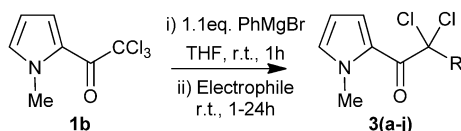


Fig. 2 Proposed reaction pathways.

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



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

^a **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. ^b Isolated yields. ^c 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).¹⁶

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 α,α -dichloro ketones. 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).¹⁷

In conclusion we have demonstrated a new approach to functionalised α,α -dichloro ketones, *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 α,α -dichloro ketones formed will be discussed in future publications.

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- 13 Trace 2-phenyltetrahydrofuran could also be detected by ¹H NMR and GCMS, when reactions were carried out in THF. We postulate that this is formed through radical H abstraction from the α -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 C₆H₅Cl nor C₆H₅Br (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 MgCl₂. The enolate was reacted with D₂O to give a 78% yield (84% deuterium incorporation by ¹H NMR) of (2-*d*)-**2b** or 4-NO₂(C₆H₄)CHO to give a 47% yield of **3f**.