

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

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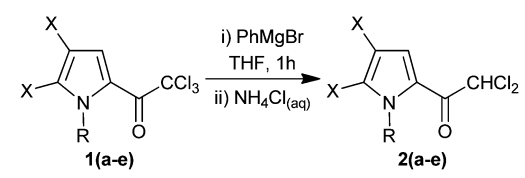
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2,2,2-Trichloro-1-arylethanones undergo high yielding reductions to the corresponding 2,2-dichloro-1-arylethanones in the presence of RMgX. A single electron transfer mechanism for the reaction is proposed based on trapping experiments. Reaction of the intermediate enolates with a range of electrophiles is described, providing a convenient route to substituted 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 NH_4Cl .

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 NH_4Cl , 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.

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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

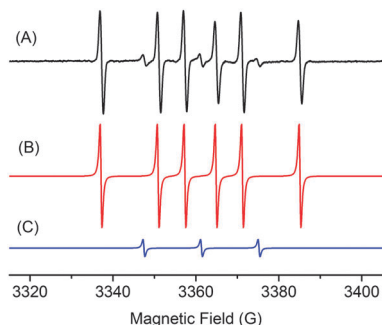


Fig. 1 (A) X-band EPR spectrum at 270 K of a THF solution resulting from the reaction of PhMgBr with ketone **1b**, in the presence of DMPO; (B) simulated spectrum of the Ph-DMPO adduct with the parameters: $g = 2.0096$; $a(^1\text{H}) = 20.3$ G and $a(^{14}\text{N}) = 13.87$ G; (C) simulated spectrum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

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

Ar-C(=O)CCl ₃ $\xrightarrow[\text{ii) D}_2\text{O}]{\text{i) 1.1 eq. PhMgBr, THF, r.t., 1h}}$ Ar-C(=O)CDCl ₂ 1(b,f,g) $\xrightarrow{\hspace{1.5cm}}$ 2(b,f,g)			
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

Ar-C(=O)CCl ₃ $\xrightarrow[\text{ii) NH}_4\text{Cl(aq)}]{\text{i) 1 eq. RMgX, THF, r.t., 1h}}$ Ar-C(=O)CHCl ₂ + R–R 1(b,f,g) $\xrightarrow{\hspace{1.5cm}}$ 2(b,f,g)					
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-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-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

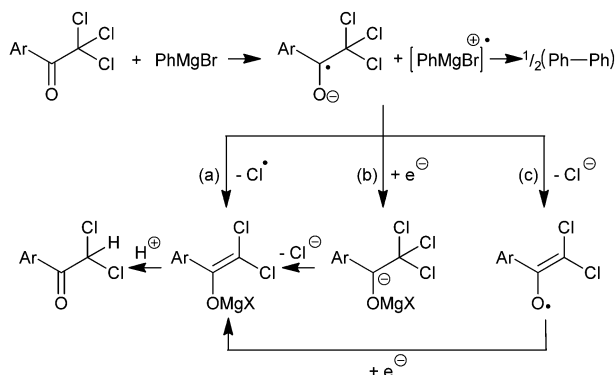


Fig. 2 Proposed reaction pathways.

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 -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 α,α -dichloroketones formed will be discussed in future publications.

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Notes and references

- 1 F. Bellesia, F. Ghelfi, F. Reverberi, F. Danna, V. Frenna, F. Felluga, A. F. Parsons and D. Spinelli, *Synthesis*, 2012, 605; Z. Chen, B. Zhou, H. Cai, W. Zhu and X. Zou, *Green Chem.*, 2009, **11**, 275; R. Akula, M. Galligan and H. Ibrahim, *Chem. Commun.*, 2009, 6991; J.-J. Kim, D. H. Kweon, S.-D. Cho, H.-K. Kim, S.-G. Lee and Y.-J. Yoon, *Synlett*, 2006, 194; R. V. Hoffman, W. S. Weiner and N. Maslouh, *J. Org. Chem.*, 2001, **66**, 5790.
- 2 Y. Zhang, K. Shibatomi and H. Yamamoto, *J. Am. Chem. Soc.*, 2004, **126**, 15038.
- 3 G. Quintanilla, I. Pérez, L. Zákova, C. Uth and F. Barba, *Eur. J. Org. Chem.*, 2011, 4681; T. Imanishi, Y. Fujiwara, Y. Sawama, Y. Monguchi and H. Sajiki, *Adv. Synth. Catal.*, 2012, **354**, 771.
- 4 H. Sasai, S. Arai and M. Shibasaki, *J. Org. Chem.*, 1994, **59**, 2661; R. Imashiro and T. Kuroda, *J. Org. Chem.*, 2003, **68**, 974.
- 5 C. Roche, K. Kadleciková, A. Veyron, P. Delair, C. Philouze, A. E. Greene, D. Flot and M. Burghammer, *J. Org. Chem.*, 2005, **70**, 8352.
- 6 D. Yang, Y.-L. Yan, B.-F. Zheng, Q. Gao and N.-Y. Zhu, *Org. Lett.*, 2006, **8**, 5757.
- 7 Z. T. Narumi, T. Kobayakawa, H. Aikawa, S. Seike and H. Tamamura, *Org. Lett.*, 2012, **14**, 4490; D. K. Barma, A. Kundu, H. Zhang, C. Mioskowski and J. R. Falck, *J. Am. Chem. Soc.*, 2003, **125**, 3218.
- 8 D. Yang, M. Yang and N.-Y. Zhu, *Org. Lett.*, 2003, **5**, 3749.
- 9 G. R. Lawton, H. Ji, P. Martásek, L. J. Roman and R. B. Silverman, *Beilstein J. Org. Chem.*, 2009, **5**, No. 28; F. Serra, P. Coutrot, M. Estève-Quelquejeu, P. Herson, T. K. Olszewski and C. Grison, *Eur. J. Org. Chem.*, 2011, 1841.
- 10 H. Wack, A. E. Taggi, A. M. Hafez, W. J. Drury III and T. Lectka, *J. Am. Chem. Soc.*, 2001, **123**, 1531.
- 11 N. Rahn and M. Kalesse, *Angew. Chem., Int. Ed.*, 2008, **47**, 597.
- 12 E. C. Ashby and A. B. Goel, *J. Am. Chem. Soc.*, 1981, **103**, 4983; E. C. Ashby, *Pure Appl. Chem.*, 1980, **52**, 545; E. C. Ashby, *Acc. Chem. Res.*, 1988, 414.
- 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.
- 14 Commercial PhMgBr was shown to contain <2 mg of Ph₂ per mmol.
- 15 J. Villieras and B. Castro, *Bull. Soc. Chim. Fr.*, 1970, **3**, 1189; K. Maruyama, Y. Matano and T. Katagiri, *J. Phys. Org. Chem.*, 1991, **4**, 501.
- 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**.