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

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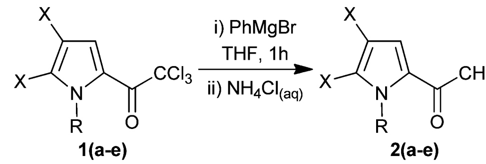
2,2,2-Trichloro-1-arylethanones undergo high yielding reductions to the corresponding 2,2-dichloro-1-arylethanones in the presence of RMgX. A single electron transfer mechanism for the reaction is proposed based on trapping experiments. Reaction of the intermediate enolates with a range of electrophiles 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 reactions[4] 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 esters[8] and heteroaromatics,[9] have been used as chlorinating agents[10] 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. 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.

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.

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 ^{13}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

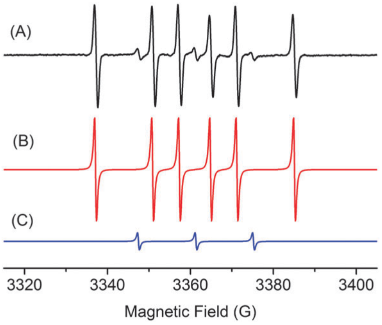


Fig. 1 (A) X-band EPR spectrum at 270 K of a THF solution resulting from the reaction of PhMgBr with ketone **1b**, in the presence of DMPO; (B) simulated spectrum of the Ph–DMPO adduct with the parameters: g = 2.0096; $a(^1H)$ = 20.3 G and $a(^{14}N)$ = 13.87 G; (C) simulated spectrum of the Ph_2–DMPO adduct, with g = 2.0095 and $a(^{14}N)$ = 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 N_2. 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 ^{14}N hyperfine coupling constants: $a(^1H)$ = 20.3 G and $a(^{14}N)$ = 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, $a(^{14}N)$ = 13.87 G). In the absence of ketone **1b** neither adduct was observed, indicating that the Ph radical is generated under the reaction conditions.

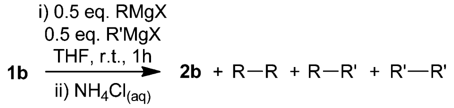
To further probe 1,1′-biphenyl formation we examined the reaction between ketone **1b** and a number of other RMgX species, where R was a *para*-substituted phenyl group (Table 2).

Reaction of 4-Me(C_6H_4)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 regents (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_4Cl to give the observed reduction product. To confirm this, ketones **1b**, **1f** and **1g** were reacted with PhMgBr and quenched with D_2O 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).

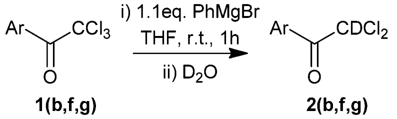
Table 2 Reaction of RMgX/R′MgX with ketone **1b**



Entry	RMgX	R′MgX	Yields[a] (%)		
			R–R	R–R′	R′–R′
1	4-Me(C_6H_4)MgI	4-Me(C_6H_4)MgI	66	—	—
2	4-Me(C_6H_4)MgI	PhMgI	14[b]	24[b]	23
3	4-MeO(C_6H_4)MgI	4-Me(C_6H_4)MgI	43	0	16
4	4-MeO(C_6H_4)MgBr	PhMgBr	0	43	20

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

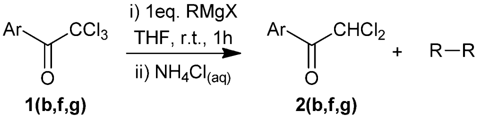
Table 3 Reaction trapping with D_2O



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

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

Table 4 Influence of R and X substituents



Entry	R	X	Ar	Yield/2[a] (%)	Yield/R_2[b] (%)
1	Et	Br	1-Methyl-1*H*-pyrrol-2-yl (**1b**)	50	nd
2	i-Pr	Cl	1-Methyl-1*H*-pyrrol-2-yl (**1b**)	42	nd
3	Ph	Cl	1-Methyl-1*H*-pyrrol-2-yl (**1b**)	61	45
4	Ph	Br	1-Methyl-1*H*-pyrrol-2-yl (**1b**)	94	52
5	Ph	I	1-Methyl-1*H*-pyrrol-2-yl (**1b**)	94	62
6	Et	Br	*p*-Tolyl (**1f**)	33	nd
7	i-Pr	Cl	*p*-Tolyl (**1f**)	33	nd
8	Ph	Cl	*p*-Tolyl (**1f**)	47	35
9	Ph	Br	*p*-Tolyl (**1f**)	68	38
10	Ph	I	*p*-Tolyl (**1f**)	96	71
11	Ph	Br	1-(4-(*tert*-Butyl)phenyl) (**1g**)	71	39
12	Ph	I	1-(4-(*tert*-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, Et_2O 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

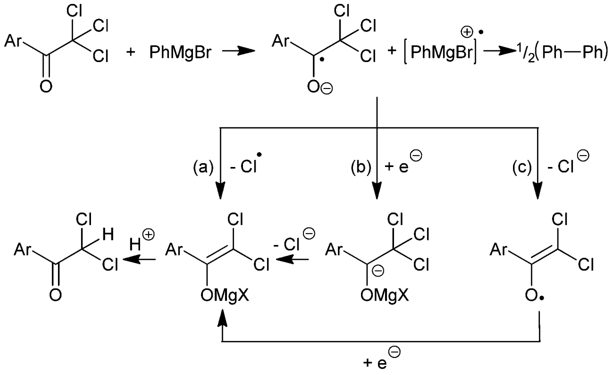
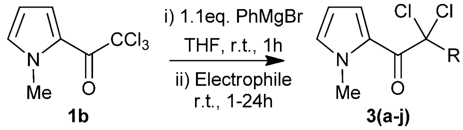


Fig. 2 Proposed reaction pathways.

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



Product[a]	Electrophile	R	Yield[b] (%)
3a	PhCHO	PhCH(OH)	81[c]
3b	4-MeO(C_6H_4)CHO	4-MeO(C_6H_4)CH(OH)	85[c]
3c	4-I(C_6H_4)CHO	4-I(C_6H_4)CH(OH)	94
3d	5-Me(C_4H_2O)CHO	5-Me(C_4H_2O)CH(OH)	70
3e	C_6F_5CHO	C_6F_5CH(OH)	70
3f	4-NO_2(C_6H_4)CHO	4-NO_2(C_6H_4)CH(OH)	96[c]
3g	4-NO_2(C_6H_4)CH_2Cl	4-NO_2(C_6H_4)CH_2	37[c]
3h	4-NO_2(C_6H_4)COCl	4-NO_2(C_6H_4)C(O)	95[c]
3i	(EtO_2C)$_2$CO	(EtO_2C)$_2$C(OH)	75
3j	C_6H_5COCl	C_6H_5C(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-1*H*-pyrrol-2-yl)ethanone (**1b**) to give substituted α,α-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).[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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13 Trace 2-phenyltetrahydrofuran could also be detected by ^{1}H 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 C_6H_5Cl nor C_6H_5Br (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 $MgCl_2$. The enolate was reacted with D_2O to give a 78% yield (84% deuterium incorporation by ^{1}H NMR) of (2-*d*)-**2b** or 4-NO_2(C_6H_4)CHO to give a 47% yield of **3f**.