ChemComm

COMMUNICATION

RSCPublishing

View Article Online View Journal | View Issue

Cite this: Chem. Commun., 2013, 49, 2756

Received 21st December 2012, Accepted 19th February 2013

DOI: 10.1039/c3cc39147g

www.rsc.org/chemcomm

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

Ali H. Essa,^{ab} Reinner I. Lerrick,^{ac} Floriana Tuna,^d Ross W. Harrington,^a William Clegg^a and Michael J. Hall^{*a}

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 silvl enolates,² electrochemical or metal mediated reductions,³ aldol reactions⁴ or cycloadditions with dichloroketene.⁵ a, a-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-(1H-pyrrol-2-yl)ethanone (1a) to PhMgBr, followed by quenching with excess aqueous NH₄Cl.

^a School of Chemistry, Bedson Building, Newcastle University, Newcastle upon Tyne, NE1 7RU, UK. E-mail: m.hall@ncl.ac.uk; Fax: +44 (0)191 222 6929; Tel: +44 (0)191 222 7321 

Entry	R	Х	PhMgBr	Temp.	Product	Yield ^{b} (%)
1	Н	Н	1.1 eq.	0 °C	2a	50
2	Н	н	1.1 eq.	r.t.	2a	55
3	Н	Н	2.2 eq.	r.t.	2a	90
4	Me	н	1.0 eq.	r.t.	2b	94
5	Н	Cl	2.0 eq.	r.t.	2 c	87
6	Н	Br	2.0 eq.	r.t.	2 d	95
7	Н	Ι	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.

^b Department of Chemistry, College of Science, University of Basrah, Basrah, Iraq

^c School of Chemistry, Nusa Cendana University, Indonesia

^d School of Chemistry and Photon Science Institute, The University of Manchester, Oxford Road, Manchester, M13 9PL, UK

[†] 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; $a(^{1}H) = 20.3$ G and $a(^{14}N) = 13.87$ G; (C) simulated spectrum of the Ph₂–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 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: $a(^{1}H) = 20.3$ 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).

	i) 0.5 eq. RMgX 0.5 eq. R'MgX 1b	2b + R—R + R—I	R' + R'-	—R'	
			Yields	$s^{a}(\%)$	
Entry	RMgX	R'MgX	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	$4-MeO(C_6H_4)MgBr$	PhMgBr	0	43	20
^{<i>a</i>} Isolated vields. ^{<i>b</i>} Products not separable, vield determined by GC-MS.					

 Table 3
 Reaction trapping with D2O

Ar CCl ₃) 1.1eq. PhMgBr THF, r.t., 1h ii) D ₂ O		
1(b,f,g)		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>)-2 b	86	89
<i>p</i> -Tolyl	(2-d)-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

	i) 1eq. RMgX		
Ar CCl ₃	THF, r.t., 1 <u>h</u>	Ar CHCl ₂	
II O	ii) NH ₄ Cl _(aq)		K K
1(b,f,g)		2(b,f,g)	

Entry	R	х	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	\mathbf{Cl}	1-Methyl-1 <i>H</i> -pyrrol-2-yl (1b)	42	nd
3	Ph	\mathbf{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	Ι	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	\mathbf{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	Ι	<i>p</i> -Tolyl (1f)	96	71
11	Ph	Br	1-(4-(<i>tert</i> -Butyl)phenyl) (1g)	71	39
12	Ph	Ι	1-(4-(<i>tert</i> -Butyl)phenyl) (1g)	98	58
^a Isolated yields ^b Yield based on total RM α X 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 ₆ H 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 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	$4-NO_2(C_6H_4)CHO$	$4-NO_2(C_6H_4)CH(OH)$	96 ^c
3g	$4-NO_2(C_6H_4)CH_2Cl$	$4-NO_2(C_6H_4)CH_2$	37 ^c
3ĥ	4-NO ₂ (C ₆ H ₄)COCl	$4-NO_2(C_6H_4)C(O)$	95 ^c
3i	$(EtO_2C)_2CO$	$(EtO_2C)_2C(OH)$	75
3ј	C ₆ H ₅ COCl	$C_6H_5C(O)$	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-aryl-ethanones. Additional examination of the substrate scope and

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

The authors thank the Iraqi Ministry of Education (A.H.E.) and the Indonesian Ministry of National Education (R.I.L.) for funding, ESPRC for X-ray facilities at Newcastle (EP/F03637X/1), the EPSRC National EPR Facility, the EPSRC National Mass Spectrometry Service, Prof. W. McFarlane and Dr C. Wills (NCL) for NMR support, and O. Aslan, M. Dunn, A. Nag and E. Çiftçi (NCL) for synthesis of **1d–g**.

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- 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**.