Pergamon

SCIENCE DIRECT®

Tetrahedron Letters 44 (2003) 5653–5656

TETRAHEDRON LETTERS

Regiochemical observations on the lithiation of 1,2,4-trichlorobenzene and reaction with DMF and oxamide electrophiles in THF

Andrew J. Burton,[a,*] Kevin S. Cardwell,[a] Matthew J. Fuchter,[a] Mika K. Lindvall,[c] Rajnikant Patel,[b] Terry W. Packham,[b] Jeremy C. Prodger,[a] Mark B. Schilling[a] and Matthew D. Walker[a]

[a]*GlaxoSmithKline R&D, Chemical Development, Medicines Research Centre, Stevenage, Hertfordshire SG1 2NY, UK*
[b]*GlaxoSmithKline R&D, Process Technologies, Temple Hill, Dartford, Kent DA1 5AH, UK*
[c]*GlaxoSmithKline R&D, Computational and Structural Sciences, Medicines Research Centre, Stevenage, Hertfordshire SG1 2NY, UK*

Received 23 April 2003; accepted 30 May 2003

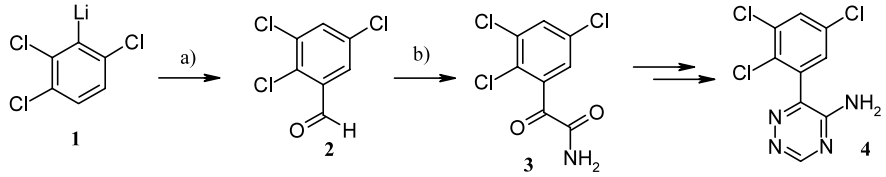
This paper is dedicated to the late David Collier

Abstract—Unusual regiochemistry is observed in the products arising from the reaction of lithiated 1,2,4-trichlorobenzene with *N*,*N*-dimethylformamide and tetraalkyloxamides.

The α-keto amide **3** is a key intermediate in the synthesis of the sodium channel blocker GW356194 **4**.[1] The synthesis of **3** has involved conversion of 2,3,5-trichlorobenzaldehyde **2** into **3** via a four stage procedure that uses both oxidising conditions and cyanide chemistry (Scheme 1). We present here the results of our investigations into the regiochemistry and mechanism of the reaction of lithiated 1,2,4-trichlorobenzene **1** with *N*,*N*-dimethylformamide (DMF). In addition we report a new, one-step synthesis of the α-keto amides **12**, **13** and **14** for use as intermediates in the synthesis of GW356194 **4**.

The chloro substituents in 1,2,4-trichlorobenzene combine to make the anion in the 3-position the most stable and this can be demonstrated by deuteration (Scheme 2). However, when a THF solution of anion **1** is reacted with 5 equiv. DMF at −78°C and allowed to warm slowly to room temperature the unexpected 2,3,5-trichlorobenzaldehyde regioisomer **2** is the major reaction product, accompanied by a small amount of the 2,4,5-trichlorobenzaldehyde **8** (conditions b). Conversely, if the reaction is quenched without aging then the expected 2,3,6-trichlorobenzaldehyde **7** predominates (Scheme 2) and can be isolated in 50% yield (conditions c).[2] Detailed distributions of isomers (as judged by capillary GC) as the reaction is warmed to room temperature are reported in Table 1.

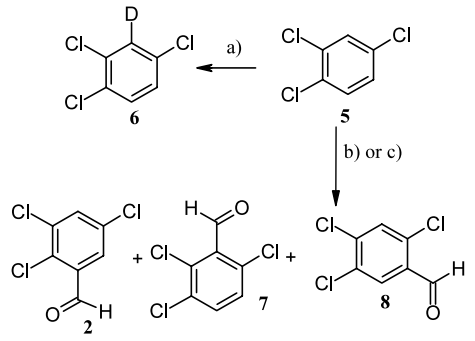
The reaction of tetramethyloxamide with organolithium compounds has been described for the direct synthesis α-keto amides.[3] We wanted to see if lithiated 1,2,4-



Scheme 1. *Reagents and conditions*: (a) DMF (5 equiv.), THF, −78°C–rt, 76%; (b) (i) $NaMnO_4$, NaOH, 85%; (ii) oxalyl chloride, toluene; (iii) CuCN, CH_3CN; (iv) 4 M HCl in 1,4-dioxane, 1 equiv. H_2O, 55% (three stages).

Keywords: organolithium; 1,2,4-trichlorobenzene; 2,3,5-trichlorobenzaldehyde; α-keto amide.
* Corresponding author. Tel.: +44 1438 763667, fax: +44 1438 764869; e-mail: andrew.j.burton@gsk.com

0040-4039/$ - see front matter © 2003 Elsevier Ltd. All rights reserved.
doi:10.1016/S0040-4039(03)01360-1



Scheme 2. *Reagents and conditions*: (a) (i) *n*BuLi, THF, −78°C, (ii) D_2O; (b) (i) *n*BuLi, THF, (ii) DMF (5 equiv.), −78°C–rt, (iii) H_2O; (c) (i) *n*BuLi, THF, (ii) DMF (5 equiv.), −78°C, (iii) H_2O.

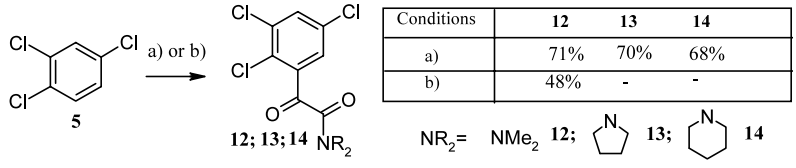
Table 1.

Time (h)	*T* (°C)	Ratio of isomers		
		2,3,5 (**2**)	2,4,5 (**8**)	2,3,6 (**7**)
1.5	−65	0	0	100
2.5	−40	42	4	50
4	−20	88	7	5
6	15	92	7	0
20	20	92	7	0

trichlorobenzene would react with oxamides to give α-keto amides with the correct regiochemistry for use as synthons in the synthesis of GW356194 **4** and we were delighted to find that reaction of **1** with oxamides **9**, **10** and **11** gave rise to the α-keto amides **12**, **13** and **14**, respectively (Scheme 3, conditions a).[4] However, we were surprised to find that this reaction did not show the same temperature dependence as the reaction of **1** with dimethylformamide and none of the 2,3,6-isomer could be isolated as demonstrated for oxamide **9** (Scheme 3, conditions b). Also, none of the 2,4,5 isomers were observed.

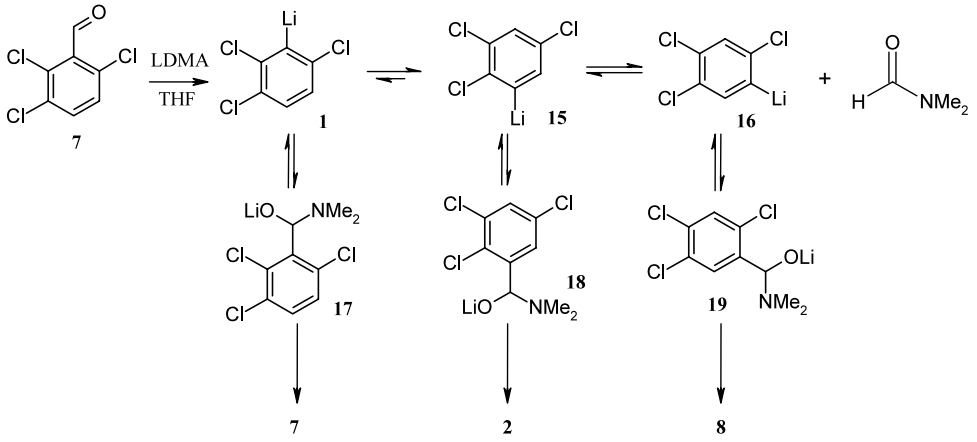
We envisaged that our observations for the reaction with oxamides compared to DMF could be explained by operation of a different reaction pathway. In the formylation reaction, we propose that the adduct **17** is formed in the 3-position and then rearranges. In order to probe this mechanistic hypothesis we decided to carry out labelling studies to see if the rearrangement of the DMF adduct was inter- or intramolecular. Therefore we looked for a way of generating the adduct **17** that ensured it would be the only reactive species in solution. Thus, 2,3,6-trichlorobenzaldehyde **7** was treated with lithium dimethylamide (LDMA) and the composition of the resulting reaction mixture was determined by HPLC. On addition of LDMA we observed rapid conversion to trichlorobenzene, indicating that the aldehyde had decomposed to give lithiated trichlorobenzene **1**, presumably via adduct **17**, and DMF. The lithiated trichlorobenzene then gradually reacted with the DMF over 18 h to give a mixture of 2,3,5- and 2,4,5-trichlorobenzaldehyde **2** and **8**, respectively.

Although not useful for adduct regeneration this result suggests an intermolecular rearrangement mechanism in which the adducts are in equilibrium with lithiated



Conditions	12	13	14
a)	71%	70%	68%
b)	48%	-	-

Scheme 3. *Reagents and conditions*: (a) (i) *n*BuLi, THF, −78°C, (ii) $R_2N(CO)_2NR_2$ (NR_2 = NMe_2 **9**; *N*-pyrrolidyl **10**; *N*-piperidyl **11**), −78°C–0°C, (iii) $NaHCO_3$ (aq.); (b) (i) *n*BuLi, −78°C, (ii) **9** −78°C/6 h, (iii) $NaHCO_3$ (aq.) (−78°C).



Scheme 4.

trichlorobenzene and DMF, with the mixture gradually equilibrating to give the thermodynamically most favourable adducts (Scheme 4). This suggestion was further supported by the incorporation of a deuterium label on addition of D_7-DMF to the mixture and by a double crossover experiment (Scheme 5).[5] Three of the four labelled components were observed directly by selective HMBC experiments and the fourth by comparison with the coupled ^{13}C NMR spectrum.

In reaction with the more sterically demanding oxamides initial reaction at the 3-position appears not to take place and we suggest that the anion **1** is in equilibrium with **15** and reaction only takes place with the less sterically hindered anion.[6] This suggestion was supported by our observation that both 1,3-dichlorobenzene[8] and 1,3,5-trichlorobenzene could be formylated between the two chlorine atoms but showed no reactivity towards oxamides. An analogous crossover experiment using the α-keto amide **13**, D_9-**13** and lithum pyrrolidyl amide was also carried out but this led only to 2% deuterium crossover, as estimated by high accuracy mass spectrometry.

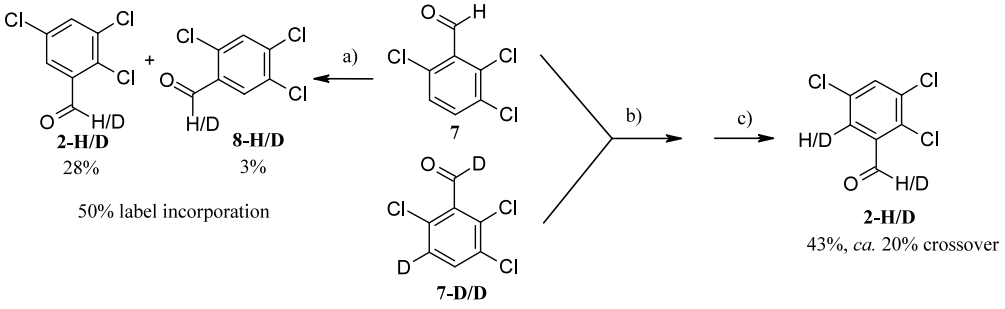
In addition, the structures and energies of the regioisomers of the aromatic anions, DMF adduct anions and products were determined via a quantum chemical approach.[9] The energies of each regioisomeric series are shown in Figure 1. The values are consistent both with the temperature dependence of the product distribution and with the product distribution itself at room temperature.

Thus, while anion formation between the two chlorines is favoured energetically, the corresponding product is disfavoured, accounting for the opposite temperature dependence trend between the 2,3,6 isomer and the other two regioisomers. At low temperatures and short reaction times, the relative stability of the aromatic anions seems to dominate the product distribution. Longer reaction time and warming to room temperature may allow extensive equilibration between the regioisomeric adducts, and the relative energies of adducts, modelled in THF, are broadly in line with the relative ratio of 2,3,5, 2,4,5 and 2,3,6 isomers.

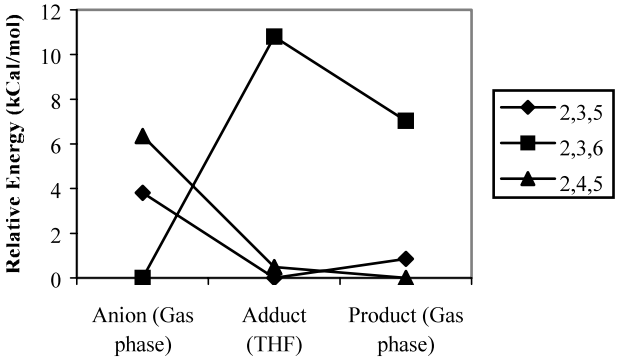
In conclusion we have demonstrated that lithiated 1,2,4-trichlorobenzene is a valuable intermediate for the one-step synthesis of 2,3,5 substituted α-keto-amides when reacted with tetra-alkyloxamides and it is likely that the reaction proceeds via a different mechanism to the known synthesis of 2,3,5-trichlorobenzaldehyde.

Acknowledgements

We would like to thank Peter Moore and Alec Simpson for assistance in obtaining NMR and mass spectra for the crossover experiments.



Scheme 5. *Reagents and conditions*: (a) (i) LDMA, –78°C, THF, 30 min, (ii) D_7 DMF 1 equiv., (iii) –78°C–rt, (iv) H_2O; (b) (i) LDMA, –78°C, THF, 30 min; (c) (i) –78°C–rt over ca. 20 h, (ii) H_2O.



Isomer	Relative Energy (kCalmol^{-1})	Relative Energy (kCalmol^{-1})	Relative Energy (kCalmol^{-1})
	Anion (Gas phase)	Adduct (THF)	Product (Gas phase)
2,3,5	3.8	0	0.9
2,3,6	0	10.8	7.0
2,4,5	6.4	0.5	0

Figure 1.

References

1. PCT Int. Appl. (1999), WO 9932462 A1.
2. PCT Int. Appl. (1995), WO 9507877 A1.
3. Campaigne, E.; Skowronski, G.; Rogers, R. B. *Synth. Commun*. **1973**, *3*, 325.
4. All new compounds gave concordant ^{1}H, ^{13}C NMR and mass spectral analyses.
5. Deuterated trichlorobenzen2e, for the synthesis of **7-D**/**D**, was obtained from the corresponding Grignard reagent, suggesting that these reagents do not display the same anion equilibration.
6. Schlosser and co-workers have derived a set of coefficients to determine the acidity of chlorinated benzene aromatics.[7] Using their predictions, the 2,3,5-isomer should be the next most stable anion after the 2,3,6-isomer. This is supported by our observations.
7. Schlosser, M.; Marzi, E.; Cottet, F.; Büker, H. H.; Nibberling, N. M. M. *Chem. Eur. J*. **2001**, *7*, 3511.
8. Kress, T. H.; Leanna, M. R. *Synthesis* **1988**, 803.
9. All low energy conformers for all starting materials, adduct anions and product isomers were located using Low Mode Conformational Searching and the MMFF force field in the gas phase, as implemented in MacroModel v. 7.0 (Schrodinger, Inc.). The resulting conformers were further optimised at the B3LYP/6-31+G* level using Gaussian98 A.7 (Gaussian, Inc., Pittsburgh, PA, 1998), and the energies of the adduct anions in THF (using gas phase geometries) were calculated using Tomasi's PCM solvation model. The lowest energy conformer of each isomer was considered in energy comparisons between isomers.