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Rearrangement during halogenation of 2-hydroxy-1,2-diphenylpropan-1-one (α-methylbenzoin)

Kati M. Aitken, R. Alan Aitken *

EaStCHEM School of Chemistry, University of St Andrews, St Andrews, Fife KY16 9ST, UK

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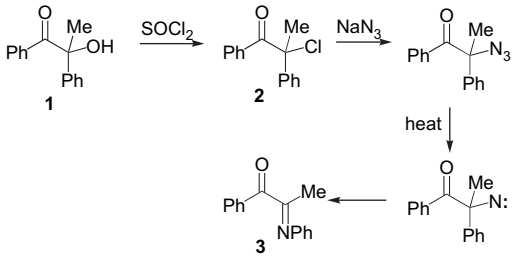
ABSTRACT

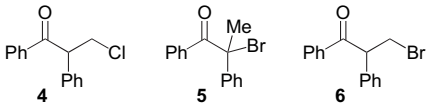
The reaction of 2-hydroxy-1,2-diphenylpropan-1-one **1** with $SOCl_2$ or PBr_3 gives, respectively, the 3-chloro- and 3-bromo-1,2-diphenylpropan-1-ones **4** and **6**. The expected 2-chloro- and 2-bromo-1,2-diphenylpropan-1-ones **2** and **5** can, however, be formed by treatment of 1,2-diphenylpropan-1-one **8** with Cl_2 or $Br_2/AlCl_3$. The four halogenated products are characterised by ^1H and ^{13}C NMR spectroscopy for the first time.

1. Introduction

We recently required the monoimines of unsymmetrical 1,2-diketones and were attracted by a procedure described by Boyer and Straw in 1953,[1] involving conversion of the α-hydroxyketone **1** into its chloride **2** followed by reaction with sodium azide and thermal decomposition with rearrangement to give the product **3**.



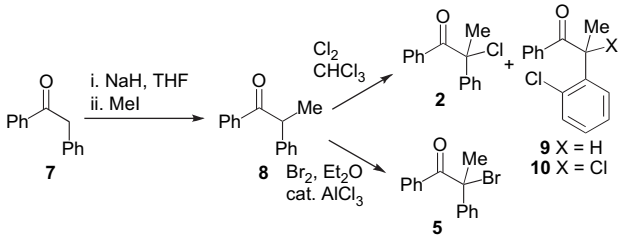
In the event, treatment of **1** with thionyl chloride gave a product that was clearly not **2** and was readily shown by ^1H and ^{13}C NMR to have the isomeric structure **4**. The fact that, contrary to an earlier report,[2] treatment of **1** with $SOCl_2$ gives **4** and not **2** was already demonstrated as early as 1955,[3] and it was not until 1970 that a genuine route to **2** appeared.[4]



A similar confusion exists in the literature for the bromination of **1** using PBr_3, which was first reported to give **5**,[5] but this result was later found to be irreproducible,[6] and the fact that the product is actually **6** does not seem to have been clearly stated so far. The synthesis of **5** was only reported in 1987.[7] Most striking is the fact that NMR spectroscopic data have apparently never been published for any of the compounds **2**, **4**, **5** or **6**. In an attempt to clarify this area we describe in this paper a reinvestigation of these reactions using modern analytical techniques, especially NMR spectroscopy.

2. Results and discussion

Authentic samples of the two non-rearranged halides **2** and **5** were first prepared by treatment of the α-methylketone **8**, prepared from deoxybenzoin **7** by methylation,[8] with the appropriate halogen (Scheme 1). Chlorination resulted in formation of some ring-chlorinated products and, in common with the literature procedure,[4] we had to resort to chromatography to obtain a pure sample of **2**. In fact ^1H NMR analysis of the reaction product after chlorination of **8** for 14 h showed the presence of **2** (40%), unreacted **8** (30%) and two ring-chlorinated products (each 15%). While simple column chromatography was sufficient to separate **2**



Scheme 1. Formation of compounds **2** and **5**.

* Corresponding author.
E-mail address: raa@st-and.ac.uk (R. Alan Aitken).

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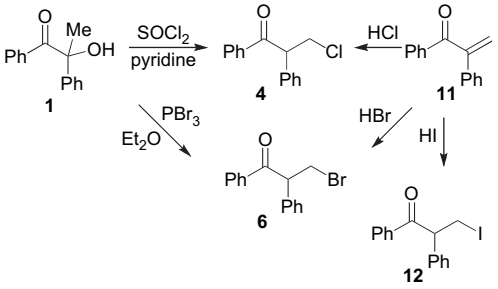
and **8** from the ring-chlorinated products, the latter were very similar to each other and were only separable using preparative HPLC. This allowed isolation of the previously unknown *o*-chloro compound **9** in pure form, and a second component, which was contaminated with some **9** but could be identified as the corresponding dichloro compound **10**. Interestingly there was no trace of the known *p*-chloro analogue of **9**.[9]

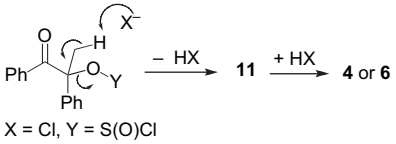
The bromination was much cleaner and proceeded readily using Br_2 with catalytic $AlCl_3$ to afford **5** but since neither the original work,[7] nor later reports mention any analytical or spectroscopic data for this compound, it was fully characterised.

We next examined halogenation of **1**, readily obtained by addition of methylmagnesium iodide to benzil.[10] Treatment with thionyl chloride in the presence of pyridine using the reported method,[1,11] cleanly gave the rearranged product **4** (Scheme 2), in contrast to benzoin itself, which does undergo chlorination without rearrangement under these conditions.[11] The reaction of **1** and thionyl chloride to give **4** has already been noted,[3,12] and the product is identical to that obtained by addition of HCl to the enone **11**,[3,13,14] which was in fact present as an impurity in the sample of **4** formed from **1**.[15] Reaction of **1** with PBr_3 using the method originally reported to give **5**,[5] gave a product that was obviously the rearranged bromide **6**, identical to that formed by addition of HBr to **11**.[14] With the four compounds **2**, **5**, **4** and **6** in hand, comparison of their NMR spectra left no room for doubt as to which was which. The iodide **12** has also been obtained from **11** by addition of HI,[14] and also more recently by another method resulting in NMR data being available for this iodide.[16] This allowed a detailed assignment of the spectra for **4**, **6** and **12** (Table 1) showing a good degree of agreement except for the well known shielding effect of the heavier halogens on the C-3 signal.



Scheme 2. Formation of compounds **4** and **6**.

This type of halogenation with rearrangement is relatively uncommon but some previously reported examples are shown in Scheme 3. Hudson and co-workers observed a small amount of isomerisation in the BBr_3 mediated bromination of aliphatic tertiary alcohols and ascribed this to elimination to form an alkene followed by radical addition of HBr.[17] Much earlier, the fact that treatment of acetophenone cyanohydrin with concentrated HCl gave the tropic acid derivative **14** rather than the expected atrolactinic acid derivative **15** was crucial in elucidating the structure of atropine and was again postulated to involve an intermediate



X = Cl, Y = S(O)Cl
X = Br, Y = –P<

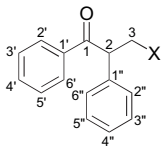


Table 1
Comparison of NMR data for **4** and **6** with that for **12**[16]

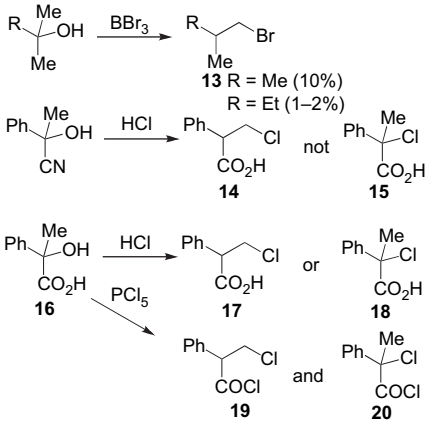
X	2-H	3-H
Cl	4.94 (dd, *J* 9.0, 5.7)	4.30 (dd, *J* 10.8, 9.0), 3.73 (dd, *J* 10.8, 5.7)
Br	5.01 (dd, *J* 9.0, 5.4)	4.16 (dd, *J* 9.9, 9.0), 3.59 (dd, *J* 9.9, 5.4)
I	5.1 (dd, *J* 9, 6)	4.0 (t, *J* 9), 3.5 (dd, *J* 9, 6)

X	C-1	C-2	C-3
Cl	196.8	55.9	45.1
Br	197.0	56.0	32.8
I	197.4	56.6	5.6

X	(1-Ph)			
	C-1′	C-2′,6′	C-3′,5′	C-4′
Cl	136.0	128.1	128.5	133.2
Br	136.8	128.1	128.6	133.3
I	138.2	128.0	128.4	133.3

X	(2-Ph)			
	C-1″	C-2″,6″	C-3″,5″	C-4″
Cl	136.0	129.1	128.6	128.0
Br	136.0	129.2	128.7	128.1
I	128.7	129.3	128.6	127.9

alkene.[18–20] Later studies showed that chlorination of atrolactinic acid **16** with HCl could give either **17** or **18**,[21,22] while treatment with PCl_5 gave products derived from **19**, as well as the expected product **20**.[22] The fact that compounds **4** and **6** are known to be formed by addition of HX to enone **9**, which is actually formed from **1** under the conditions used to convert it to **4**, and the ample literature precedent of Scheme 3, leave little doubt that it is the possibility of dehydration via the activated intermediates to give the relatively stable enone **11** that makes compound **1** behave anomalously towards attempted halogenation, as shown below.



Scheme 3. Mechanistically similar reactions.

To return to our original objective, once it became clear that the unrearranged chloride **2** could only be obtained in low yield after a difficult separation, we resorted to the direct reaction of 1-phenylpropane-1,2-dione with appropriate aromatic amines,[23] and in this way were able to prepare **3** and its previously unknown *N*-*o*-tolyl analogue.

3. Experimental

3.1. General

Infrared spectra were recorded for liquid films on a Perkin Elmer Spectrum GX instrument. NMR spectra were obtained for ^1H at

300 MHz, and for ^{13}C at 75 MHz using a Bruker Avance 500 instrument. All spectra were run on solutions in $CDCl_3$ with internal Me_4Si as reference. Chemical shifts are reported in parts per million to high frequency of the reference and coupling constants *J* are in Hertz. Mass spectra were obtained on a Micromass GCT mass spectrometer using chemical ionisation. Melting points were determined in open capillary tubes on a Gallenkamp apparatus and are uncorrected. Column chromatography was performed using silica gel of 33–70 μm particle size and preparative HPLC was carried out using a Waters system with a Phenomenex® Kingsorb 5 μ C18 column.

3.2. 2-Chloro-1,2-diphenylpropan-1-one 2

A solution of α-methyldeoxybenzoin **8** (10.0 g, 47.6 mmol) in chloroform (950 cm^3) was stirred at rt while chlorine gas was bubbled slowly through it for 14 h. Evaporation followed by chromatography of the residual liquid (SiO_2, hexane/EtOAc, 95:5) gave the product **2** (3.2 g, 28%) as a colourless oil (lit.,[4] mp 47–48 °C); ν_{max}/cm^{-1} 1688, 1597, 1490, 1447, 1375, 1253, 1183, 1055, 960, 841, 762 and 698; δ_H 2.04 (3H, s), 7.24 (2H, t, *J* 6.0), 7.27–7.45 (4H, m), 7.49 (2H, d, *J* 6.0) and 7.75 (2H, d, *J* 6.0); δ_C 33.2 (CH_3), 73.6 (C), 125.2 (2CH), 127.8 (2CH), 128.1 (CH), 128.8 (2CH), 130.8 (2CH), 132.5 (CH), 133.5 (C), 141.5 (C) and 194.2 (CO); *m*/*z* 245 ($^{35}Cl-M+H^+$, 2%), 209 ($M-Cl^+$, 100) and 105 (PhCO, 26). This was followed by a fraction containing a mixture of two ring-chlorinated products, and finally a fraction containing unreacted **8**. Preparative HPLC (5% H_2O in MeCN) of the second fraction gave first 2(2-chlorophenyl)-1-phenylpropan-1-one **9**.

*3.2.1. 2(2-Chlorophenyl)-1-phenylpropan-1-one **9***

Found: $M+H^+$, 245.0740. $C_{15}H_{14}^{35}ClO$ requires 245.0733; δ_H 1.49 (3H, d, *J* 7.0), 5.14 (1H, q, *J* 7.0), 7.13–7.17 (3H, m, Ar), 7.32–7.42 (3H, m, 3,5-H of Ph and Ar), 7.45–7.52 (1H, m, 4-H of Ph) and 7.92–7.95 (2H, m, 2,6-H of Ph); δ_C 17.8 (CH_3), 44.2 (CH), 127.5 (CH), 128.2 (CH), 128.56 (3CH), 128.59 (2CH), 129.9 (CH), 133.0 (CH and C–Cl, confirmed by HMBC), 136.0 (C-1 of Ph), 139.2 (C-1 of Ar) and 200.1 (CO); *m*/*z* (CI) 247 ($^{37}Cl-M+H^+$, 7%), 245 ($^{35}Cl-M+H^+$, 28), 243 (12) and 209 (100). This was followed by a fraction consisting mainly of 2-chloro-2-(2-chlorophenyl)-1-phenylpropan-1-one **10**.

*3.2.1.1. 2-Chloro-2-(2-chlorophenyl)-1-phenylpropan-1-one **10**.* Found: $M+H^+$, 279.0349. $C_{15}H_{13}^{35}Cl_2O$ requires 279.0343; δ_H 2.17 (3H, s), 7.15–7.45 (6H, m), 7.72–7.80 (2H, m) and 8.21–8.25 (1H, m); δ_C 29.2 (CH_3), 73.2 (C), 127.7 (CH), 127.8 (2CH), 128.1 (CH), 129.6 (CH), 130.0 (2CH), 130.9 (CH), 131.1 (C), 132.5 (CH), 133.7 (C), 139.7 (C) and 192.0 (CO); *m*/*z* (CI) 281 ($^{35}Cl_2-M+H^+$, 10%), 245 (36) and 243 (100).

3.3. 2-Bromo-1,2-diphenylpropan-1-one 5

A solution of α-methyldeoxybenzoin **8** (7.84 g, 37 mmol) in diethyl ether (150 cm^3) containing $AlCl_3$ (0.25 g, 1.85 mmol) was stirred at 0 °C while bromine (2.02 cm^3, 6.25 g, 39 mmol) was added dropwise. The resulting HBr gas was trapped in aqueous NaOH. After 3 h at rt, the colour of the Br_2 had disappeared and the solution was washed with water then brine, dried and evaporated. The resulting solid was vacuum dried to give the product (10.6 g, 98%) as faintly orange crystals, mp 59–61 °C. Found: $M+H^+$, 289.0226. $C_{15}H_{14}^{79}BrO$ requires 289.0228; ν_{max}/cm^{-1} 1677, 1595, 1447, 1369, 1252, 1231, 1047, 955, 844, 762 and 698; δ_H 2.22 (3H, s), 7.20–7.40 (6H, m), 7.47–7.52 (2H, m) and 7.75–7.80 (2H, m); δ_C 34.8 (CH_3), 68.0 (C), 126.2 (2CH), 127.7 (2CH), 128.0 (CH), 128.8 (2CH), 130.9 (2CH), 132.5 (CH), 133.4 (C), 141.7 (C) and 193.8 (CO); *m*/*z* 291 ($^{81}Br-M+H^+$, 2%), 289 ($^{79}Br-M+H^+$, 2), 210 ($M-Br+H^+$, 45), 209 ($M-Br^+$, 100), 193 (72) and 105 (PhCO, 22).

3.4. 3-Chloro-1,2-diphenylpropan-1-one 4

A suspension of α-methylbenzoin **1** (14.0 g, 62 mmol) in dry pyridine (7 cm^3) was heated until the solid dissolved and then cooled and stirred at 0 °C while thionyl chloride (6.05 cm^3, 9.87 g, 83 mmol) was added in small portions. After 1 h, water (25 cm^3) was cautiously added and the mixture was extracted with ethyl acetate (3×25 cm^3), which was dried and evaporated. The crude product (13.89 g) consisted of a mixture of **4** (70%) and the enone **11** (20%). Recrystallisation of the residue from ethanol gave the product (7.6 g, 50%) as colourless crystals, mp 57–59 °C (lit.,[3] 60 °C); ν_{max}/cm^{-1} 1683, 1597, 1493, 1448, 1339, 1235, 1176, 980, 944, 721 and 700; δ_H 3.73 (1H, dd, *J* 10.8, 5.7), 4.30 (1H, dd, *J* 10.8, 9.0), 4.94 (1H, dd, *J* 9.0, 5.7), 7.25–7.55 (8H, m) and 7.94–8.00 (2H, m); δ_C 45.1 (CH_2), 55.9 (CH), 128.0 (CH), 128.1 (2CH), 128.5 (2CH), 128.6 (2CH), 129.1 (2CH), 133.2 (CH), 135.97 (C), 136.03 (C) and 196.8 (CO); *m*/*z* 247 ($^{37}Cl-M+H^+$, 10%), 245 ($^{35}Cl-M+H^+$, 40), 209 ($M-Cl^+$, 100) and 105 (PhCO, 54).

3.5. 3-Bromo-1,2-diphenylpropan-1-one 6

A solution of α-methylbenzoin **1** (15.0 g, 66 mmol) in diethyl ether (110 cm^3) was stirred at rt while PBr_3 (9.25 cm^3, 26.3 g, 97 mmol) was added dropwise and the mixture was then heated under reflux for 4 h. The mixture was evaporated and the residue dissolved in diethyl ether (100 cm^3) and washed thoroughly with water, followed by brine, dried and evaporated. The resulting solid was recrystallised from toluene to give the product (12.0 g, 63%) as colourless crystals, mp 55–56 °C (lit.,[5] 56 °C); ν_{max}/cm^{-1} 1679, 1596, 1580, 1491, 1447, 1356, 1262, 1225, 970, 759, 697 and 646; δ_H 3.59 (1H, dd, *J* 9.9, 5.4), 4.16 (1H, dd, *J* 9.9, 9.0), 5.01 (1H, dd, *J* 9.0, 5.4), 7.25–7.55 (8H, m) and 7.9–8.0 (2H, m); δ_C 32.8 (CH_2), 56.0 (CH), 128.1 (3CH), 128.6 (2CH), 128.7 (2CH), 129.2 (2CH), 133.3 (CH), 136.0 (C), 136.8 (C) and 197.0 (CO); *m*/*z* 291 ($^{81}Br-M+H^+$, 43%), 289 ($^{79}Br-M+H^+$, 52), 209 ($M-Br^+$, 100) and 105 (PhCO, 68).

3.6. 1-Phenyl-2-(phenylimino)propan-1-one 3

A solution of 1-phenylpropane-1,2-dione (0.80 g, 5.4 mmol) and aniline (0.503 g, 5.4 mmol) in toluene (20 cm^3) was heated under reflux with a Dean–Stark trap for 6 h. Evaporation and Kugelrohr distillation of the residue gave starting materials, bp 50–70 °C/1 Torr, followed by the product (0.43 g, 36%) as a colourless liquid, bp 120 °C/1 Torr (lit.,[22] 104–106 °C/0.001 Torr); δ_H 2.18 (3H, s, Me), 6.86 (2H, dd, *J* 8.4, 1.2, 2,6-H of N–Ph), 7.16 (1H, tt, *J* 7.2, 1.2, 4-H of N–Ph), 7.39 (2H, dd, *J* 8.4, 7.2, 3,5-H of N–Ph), 7.48 (2H, dd, *J* 8.4, 7.5, 3,5-H of C–Ph), 7.60 (1H, tt, *J* 7.5, 1.5, 4-H of C–Ph) and 8.15 (2H, dd, *J* 8.4, 1.5, 2,6-H of C–Ph); δ_C 16.5, 118.8 (C-2,6 of N–Ph), 124.6 (C-4 of N–Ph), 128.2 (C-2,6 of C–Ph), 129.0 (C-3,5 of N–Ph), 130.7 (C-3,5 of C–Ph), 133.3 (C-4 of C–Ph), 134.7 (C-1 of C–Ph), 149.1 (C-1 of N–Ph), 166.7 (C=N) and 193.2 (C=O).

3.7. 1-Phenyl-2-(*o*-tolylimino)propan-1-one

A preparation exactly as above but using *o*-toluidine in place of aniline gave the product (0.74 g, 58%) as a colourless liquid, bp 150 °C/1 Torr; δ_H 2.12 (3H, s, Me), 2.17 (3H, s, Ar–Me), 6.67 (1H, dd, *J* 7.8, 1.5, 6-H of N–Ar), 7.07 (1H, td, *J* 7.5, 1.5, 4-H of N–Ar), 7.17–7.26 (2H, m, 3,5-H of N–Ar), 7.49 (2H, dd, *J* 8.4, 7.5, 3,5-H of Ph), 7.60 (1H, tt, *J* 7.5, 1.5, 4-H of Ph) and 8.17 (2H, dd, *J* 8.4, 1.5, 2,6-H of Ph); δ_C 16.8, 18.1, 117.5 (C-6 of N–Ar), 124.6 (C-5 of N–Ar), 126.4 (C-4 of N–Ar), 126.7 (C-2 of N–Ar), 128.3 (C-2,6 of Ph), 130.6 (C-3 of N–Ar), 130.7 (C-3,5 of Ph), 133.3 (C-4 of Ph), 134.8 (C-1 of Ph), 148.1 (C-1 of N-Ar), 166.7 (C=N) and 193.2 (C=O).

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