Conversion of Benzal Halides to Benzaldehydes in the Presence of Aqueous Dimethylamine

Donald Bankston*

Bayer Pharmaceuticals Corporation, Department of Chemistry Research, West Haven, CT 06516, USA
E-mail: donald.bankston.b@bayer.com

Received 8 August 2003; revised 3 November 2003

Abstract: Aqueous dimethylamine is an efficient reagent for the conversion of a variety of benzal halides to their corresponding benzaldehydes. Studies indicate that aqueous dimethylamine significantly accelerates aldehyde formation from benzal halide precursors, as compared to the use of water alone. Indeed, these reactions are routinely completed in one hour or less, depending upon substrate substitution. Desired products can be isolated in pure form, and in high yield, but silica gel filtration is often necessary to remove baseline contaminants. The method represents a novel, economical approach to acquire pure, substituted benzaldehydes from commercially available, or easily prepared starting materials.

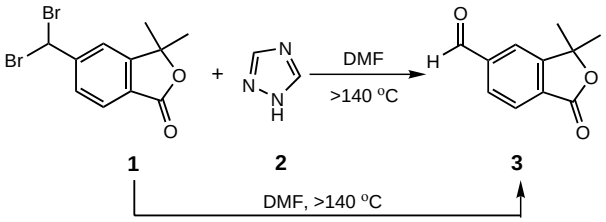
Key Words: aqueous dimethylamine, benzal halides, hydrolysis, benzaldehydes, *N*,*N*-dimethylformamide

A variety of methods are available in the literature to synthesize aldehydes.[1–9] Common preparations involve oxidation of alcohols (primary, secondary, allylic and benzylic),[2] reduction of acyl halides[3] and reduction of *N*,*N*-disubstituted amides.[4] Other, more elegant transformations have also been disclosed. For instance, a recent publication[5] describes a novel, metal-catalyzed conversion of aromatic nitriles to aldehydes in aqueous formic acid.

Hydrolysis of gem-dihalides[1] has been studied extensively. Solvolytic displacement formally involves loss of halogen with successive replacement by hydroxyl, followed by loss of water, to generate the corresponding aldehyde. The rate of hydrolysis depends upon the substrate, but the method is most applicable to benzal halides. In general, hydrolysis of dihalide aliphatics, such as dichloromethane, is quite slow, which makes the process less useful for these types of molecules. The explanation for this is related to resonance stabilization offered by the aromatics that is not possible with aliphatic systems.[1]

A new approach, conversion of benzal halides to the corresponding benzaldehydes in the presence of aqueous dimethylamine, is the focus of this report. These transformations, as well as a mechanism that supports this event, will be discussed in detail.

Heating benzal halide **1** in *N*,*N*-dimethylformamide (DMF) in the presence of 1,2,4-triazole (**2**), or its sodium salt, afforded unexpected results (Scheme 1). Observed mono- or disubstitution by triazole **2** did not occur. Instead, aldehyde **3** was isolated reproducibly. Repeating the reaction in the absence of **2** still generated **3**. A literature search indicated that benzal halides could be transformed into aldehydes by sodium iodide in anhydrous DMF,[10] but the yields were poor and sodium iodide was the documented reagent for the conversion.[11] The solvent was clearly responsible for the generation of aldehyde, but a mechanism was not transparent. ^{1}H NMR displayed an aldehyde peak after **1** was heated in deuterated *N*,*N*-dimethylformamide (DMF-d_7) for 6 hours at >140 °C. This result indicated that an intermolecular formyl transfer did not occur. Since the reactions in DMF were conducted under anhydrous conditions, water was not considered a viable competitor. Further investigation demonstrated that these conditions effectively converted other benzal halides to their corresponding benzaldehydes in good yields as well (Table 1).



Scheme 1

Table 1 Reaction of Benzal Bromides with DMF

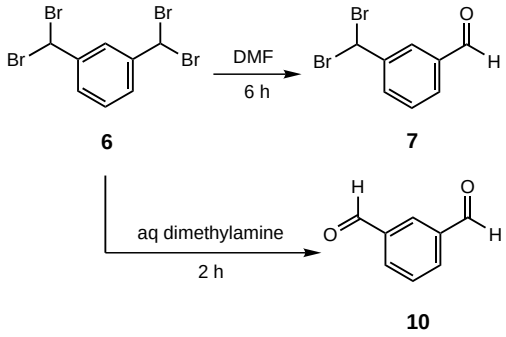
Entry	Substrate	R^1	R^2	Reaction Time (h)	Yield (%)	Product
1	**4**	H	H	6	75	**5**
2	**6**	*m*-$CHBr_2$	H	6	72	**7**
3	**8**	*m*-Cl	H	6	70	**9**

Additional studies confirmed that aldehyde formation was extremely slow, or did not occur at all, unless the reaction temperature was thermostated at or in excess of 140 °C. Under these conditions, complete reaction occurred within 5–6 hours, but chromatography was normally required to isolate pure aldehydes.

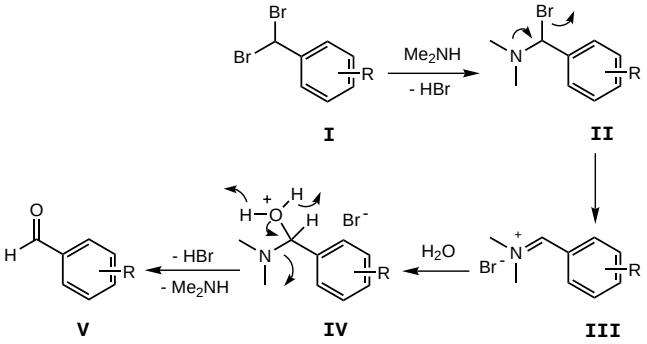
SYNTHESIS 2004, No. 2, pp 0283–0289
Advanced online publication: 18.12.2003
DOI: 10.1055/s-2003-44390; Art ID: M03603SS

Based upon all of the information collected, it appeared that the reactive species might be dimethylamine, a by-product resulting from the decomposition of DMF at elevated temperatures.[11] To test this theory, benzal bromide **1** was heated in the presence of aqueous 40% dimethylamine. Aldehyde **3** was formed in 3 hours (or less) and was isolated in 86% yield. In general, this reaction, and others, had a faster rate than those conducted in the presence of DMF. Quite possibly, this result was due to the induction period required for DMF to decompose slowly to dimethylamine at elevated temperatures. Inspection of the reactions of **6** with aqueous dimethylamine shows that both benzal halide functions were hydrolyzed to afford **10**[12,13] in at least a third of the time required to afford **7** in DMF (Scheme 2). The data collected thus far suggested that the transformation of benzal halides to their corresponding aldehydes might follow a mechanism as outlined in Scheme 3. Addition of dimethylamine to **I** would provide adduct **II**, which could rearrange to charged-imine **III**. Subsequent addition of water, followed by elimination of dimethylamine and hydrobromic acid from **IV**, effected generation of aldehyde **V**. This mechanism rationalized the results observed from these reactions, and the evidence supported a path based upon ultimate hydrolysis of a charged imine. Additional benzal bromides and commercially available benzal chlorides were treated with 40% aqueous dimethylamine to better understand the generality of these conversions (Table 2). Synthesis,[14] followed by chromatography, delivered pure benzal bromides in moderate yields (59–62%), albeit, further investigation indicated that crude benzal halide could be utilized in the hydrolysis step, since tribromide impurity, a consequence of all of these brominations, did not appear to react with aqueous dimethylamine. This was demonstrated by the reaction of **14** and **15** with 40% aqueous dimethylamine, which delivered aldehyde **16** in 70% yield (from **13**) in 15 minutes or less (Scheme 4). The advantage of this sequence stemmed from the ability to elaborate two sites in tandem in a single stage.

In general, many of the benzal halides investigated (**11**, **14**, **17**, **19**, **22** and **24**) afforded the corresponding aldehydes (**12**,[15,16] **16**, **18**,[16–19] **20**[13,15,20] and **23**[16,18,21]) in moderate to good yields in 15 minutes or less (Table 2), and the difference in reaction rates of benzal bromides versus benzal chlorides was not observed to be significant. In fact, a mixture of benzal bromide **19** and benzal chloride



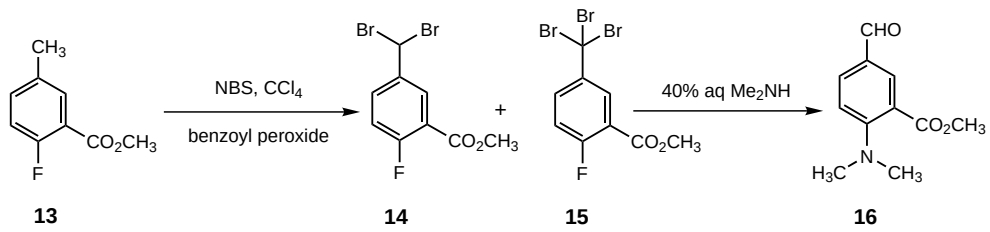
Scheme 2



Scheme 3

24 were completely hydrolyzed to aldehyde **20** in 10 minutes in the presence of aqueous dimethylamine. When the reactions of **19** and **24** were extended to 2 hours, substitution of the corresponding *p*-fluoro groups by dimethylamine occurred in good yield (>80%). At least an hour was required for complete conversions of **25** and **27** to aldehydes **26**[22,23] and **28**,[13,19,24] respectively. Extending the reaction time to 8 hours completely converted **27** to **29** (94%)[25,26] but substitution of **25** by dimethylamine to give **26a**[27] was never observed (Scheme 5).

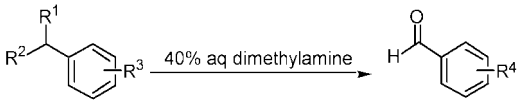
When benzal chloride **24** was stirred at room temperature in the presence of aqueous dimethylamine for 3 hours, 50% conversion to **20** occurred. This result underscored the high reactivity of these 4-fluorobenzal halides in the presence of that reagent. Even under these milder conditions, NMR analysis indicated that a trace of **21**[28,29] formed as well.



70% (overall yield for both steps)

Scheme 4

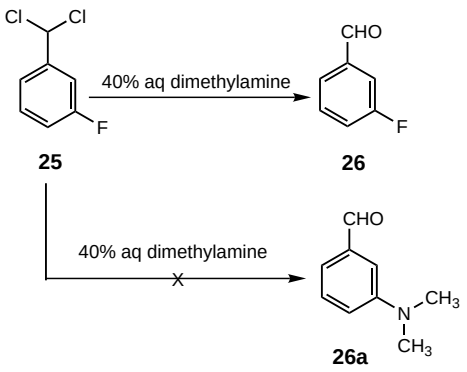
Table 2 Reactions of Benzal Halides with Aqueous Dimethylamine



n	Substrate	R^1	R^2	R^3	R^4	Reaction Time	Yield (%)	Product
1	**6**	Br	Br	*m*-$CHBr_2$	*m*-CHO	2 h	80	**10**[a]
2	**8**	Br	Br	*m*-Cl	*m*-Cl	2 h	87	**9**[a]
3	**11**	Br	Br	*m*-CO_2Me	*m*-CO_2Me	15 min	86	**12**
4	**17**	Br	Br	*m*-NO_2	*m*-NO_2	10 min	87	**18**
5	**19**	Br	Br	*p*-F	*p*-F	10 min	86	**20**
6	**19**	Br	Br	*p*-F	NMe_2	2 h	82	**21**
7	**22**	Br	Br	*m*-OMe	*m*-OMe	10 min	68	**23**
8	**24**	Cl	Cl	*p*-F	*p*-F	10 min	89	**20**
9	**24**	Cl	Cl	*p*-F	NMe_2	2 h	81	**21**
10	**25**	Cl	Cl	*m*-F	*m*-F	1 h	80	**26**
11	**27**	Cl	Cl	*o*-F	*o*-F	1 h	81	**28**
12	**27**	Cl	Cl	*o*-F	NMe_2	8 h	94	**29**

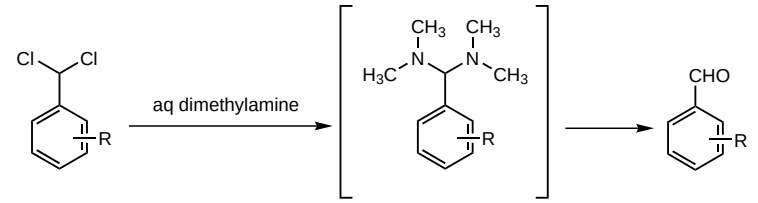
[a] Reaction times for **9** and **10** are not optimized/experiments conducted at 60 °C.

A competition experiment, in which 4-fluorobenzal chloride (**24**), 3-fluorobenzal chloride (**25**) and 2-fluorobenzal chloride (**27**) were reacted together with aqueous dimethylamine at 60 °C for an hour, provided interesting results. The conversion rate of **24** was the fastest, as expected. Inspection of an aliquot after 30 minutes indicated that **24** was completely converted to **20** (ca. 40%) and **21** (ca. 60%). In contrast, the reaction rates of **25** and **27** were considerably slower. NMR data suggested that approximately 60% of **25** and about 50% of **27** remained unreacted. After an hour of reaction time, NMR analysis indicated that all of **25** and **27** were consumed. Only a small amount of **20** persisted, as it continued to react with dimethylamine to produce **21**. A trace (ca. 10 mol%) of **29** was also suggested by the analytical results, but no evidence of **26a** was observed. This information was derived from a sample that was filtered through a plug of silica gel. However, when the crude sample was analyzed by ^1H NMR prior to its contact with silica gel a major aldehyde absorption was only observed for **21**, along with very small absorptions associated with **20**, **26** and **28**. Furthermore, two major singlets (and one very minor one) at ca. 2 ppm indicated the intermediacy of precursors that obviously collapsed to generate **26** and **28** in the presence of silica gel.



Scheme 5

Closer scrutiny of the crude mixtures resulting from the reactions of **25** and **27** suggested that the major component was **30** (**a** and **b**), where the fluorine was essentially unsubstituted (Scheme 6). The NMR data of this material indicated the presence of 12 protons (CH_3) associated with complete substitution of the dihalide moiety, as well as 4 aromatic protons with visible fluorine coupling. The conspicuous absence of a formyl signal confirmed that an aldehyde was not present. However, when the crude material was filtered through a plug of silica gel, the NMR data of the isolated products only displayed absorptions associated with **26** and **28**. Apparently, the catalytic surface of the silica gel support effected rapid conversion of that vehicle (in the presence of some moisture) to the desired aldehyde products. The collapse of these intermediates also occurred in aqueous dimethyl sulfoxide over time, but the transition was virtually instantaneous in the presence of silica gel. It appeared that **30** was a transient, but somewhat stable intermediate, that formed first from the reactions of these benzal halides with aqueous dimeth-



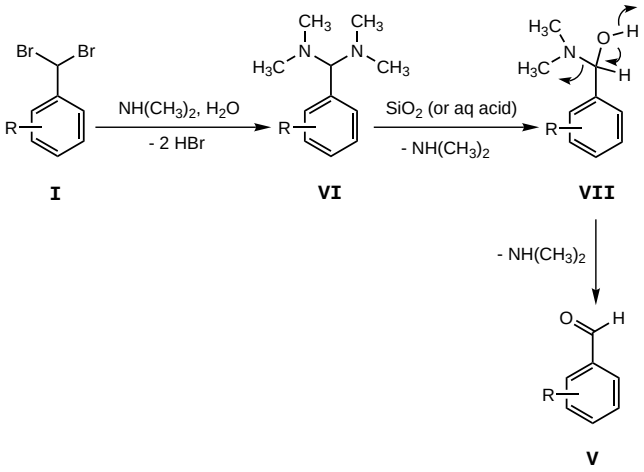
25: R = 3-F
27: R = 2-F

30a: R = 3-F
30b: R = 2-F

26: R = 3-F
28: R = 2-F

Scheme 6

ylamine. The formation of this same type of intermediate was also observed with many of the other benzal halide substrates, but not all of them. For instance, even under carefully controlled conditions, such an intermediate was never observed during the reactions of highly reactive substrates such as 4-fluorobenzal halides **19** and **24**. The ramification of this observation was a re-evaluation of the mechanism to explain the progression of all of these reactions (Scheme 7). Based upon current evidence, benzal halide **I** reacted with dimethylamine to form transient intermediate **VI**. Addition of aqueous acid (or silica gel filtration of **VI**) generated benzaldehyde **V**.



I **VI** **VII**

V

Scheme 7

The reaction of **24** with neat *N*,*N*′-dimethylethylenediamine also supported this mechanism (Scheme 8). Characterization of the isolated product (**31**) clearly showed a disubstitution of nitrogen to provide the imidazolidine. Treatment of **31** with aqueous acid or filtration through silica gel afforded **20** cleanly. This result, and others, will be the subject of a subsequent report.

A competition study with several of the benzal halides was conducted to determine their rate of hydrolysis in water as compared to aqueous dimethylamine (Table 3). In each experiment, the benzal halides were converted to their corresponding benzaldehydes substantially faster in the presence of aqueous dimethylamine versus water alone. For instance, heating benzal bromide **14** in water at

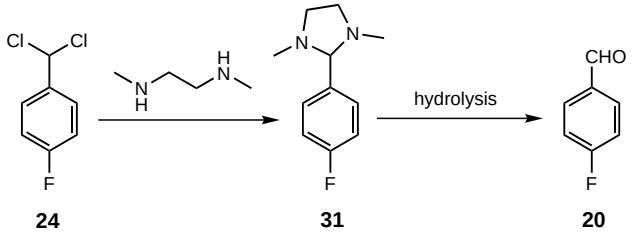
Table 3 Hydrolysis of Benzal Halides in Water vs Aqueous Dimethylamine

Substrate	Reaction Time at 60 °C in H_2O	Reaction Time at 60 °C in Me_2NH
14 + **15**	2.5 h/ca. 10 mol% **16a**[a]	15 min/70% **16**
24	4 h/ca. 50 mol% **20**	15 min/89% **20**
25	1 h/ca. 8 mol% **26**	1 h/80% **26**
27	1 h/ca. 5 mol% **28**	1 h/81% **28**

[a] Compound **16a** is not dimethylamine-substituted.

60 °C for an hour produced only a trace of fluoroaldehyde **16a**, but that substrate completely hydrolyzed, and subsequently suffered dimethylamine substitution in 15 minutes or less in the presence of aqueous dimethylamine to give **16**. Benzal chlorides **25** and **27** likewise hydrolyzed minimally (ca. 5–8 mol%) under the same conditions in water, but effectively provided high yields of aldehydes after an hour in aqueous dimethylamine.

In conclusion, aqueous dimethylamine easily transforms benzal halides to their corresponding benzaldehydes. These reactions provide pure materials in good yield after filtration through a pad of silica gel to remove baseline contaminants. In general, these conversions are quite rapid, and many are complete in 15 minutes or less. The mechanism of this novel sequence appears to evolve from a bis(dimethylamine)-substituted intermediate that collapses to the corresponding aldehyde in the presence of water and/or acidic surfaces such as silica gel.



24 **31** **20**

Scheme 8

All solvents and reagents were purchased from EM Science, Sigma-Aldrich Chemicals, Acros or Lancaster, and used without further purification. Benzal bromides **6**, **8**, **11**, **17**, **19** and **22** were prepared from the corresponding toluene derivatives using *N*-bromosuccinimide in the presence of benzoyl peroxide.[14] NMR data was obtained from a Varian 200, 300 or 400 MHz instrument. Mass spectra were done on a Finnigan LCQ ion-trap mass spectrometer with electrospray ionization and a Hewlett-Packard 1100 HPLC interface. Electron-impact mass spectra were obtained with a Hewlett Packard 5989A mass spectrometer equipped with a Hewlett Packard 5890 gas chromatograph with a J & W DB-5 column (0.25 μM coating; 30 m × 0.25 mm).

Benzaldehydes 3, 9 and 10 from Benzal Halides 1, 8, and 6 by Aqueous Acidic Workup; General Procedure

A suspension of benzal halide **1**, **8**, or **6** (0.490–3.52 mmol) in aq 40% dimethylamine (5-30 mL) was heated to 60 °C for 2–3 h under argon. The contents were then poured into CH_2Cl_2 (25–60 mL). The layers were separated, and the organic layer was washed with aq 1 N HCl (50 mL), followed by brine (2 × 50 mL). This solution was then dried (Na_2SO_4), concentrated and dried under high vacuum to afford the aldehyde **3**, **9** or **10**.

3,3-Dimethyl-1-oxo-3-hydroisobenzofuran-5-carbaldehyde (3)

Yellow crystals; yield: 86%.

^{1}H NMR ($CDCl_3$, 200 MHz): δ = 1.71 (s, 6 H, CH_3), 7.94 (m, 1 H_{arom}), 8.03 (m, 2 H_{arom}), 10.17 (s, 1 H, CHO).

GC-MS/EI): *m*/*z* = 190 (M^+).

Anal. Calcd for $C_{11}H_{10}O_3 \cdot 0.10\ H_2O$: C, 68.81; H, 5.35. Found: C, 68.84; H, 5.17.

3-Chlorobenzaldehyde (9)[15,20,30]

Yellow liquid; yield: 87%.

^{1}H NMR ($CDCl_3$, 400 MHz): δ = 7.49 (dd, *J* = 7.8, 8.0 Hz, 1 H_{arom}), 7.61 (ddd, *J* = 1.3, 1.6, 8.0 Hz, 1 H_{arom}), 7.78 (ddd, *J* = 1.3, 2.1, 7.8 Hz, 1 H_{arom}), 7.86 (dd, *J* = 1.6, 2.1 Hz, 1 H_{arom}), 9.98 (s, 1 H, CHO).

GC-MS/EI: *m*/*z* = 140 (M^+).

Benzene-1,3-dicarbaldehyde (10)[12,13]

Yellow crystals; yield: 80%.

^{1}H NMR ($CDCl_3$, 400 MHz): δ = 7.74 (dd, *J* = 7.6, 7.6 Hz, 1 H_{arom}), 8.17 (dd, *J* = 1.6, 7.6 Hz, 2 H_{arom}), 8.39 (dd, *J* = 1.6, 1.6 Hz, 1 H_{arom}), 10.12 (s, 2 H, CHO).

GC-MS/EI: *m*/*z* = 134 (M^+).

Benzaldehydes 12, 18, 23 and 28 from Benzal-Halides 11, 17, 22 and 27; Silica Gel Workup; General Procedure

A suspension of benzal halide **11**, **17**, **22**, or **27** (1.79–5.59 mmol) in 40% aq dimethylamine (5–20 mL) was heated to 60 °C under argon for 10–15 min. The crude mixture was then poured into CH_2Cl_2 (15–50 mL) and the layers were separated. The organic layer was dried (Na_2SO_4) and concentrated to a pale yellow liquid. The crude residue was filtered over silica gel (20–200 cc) equilibrated in 50% EtOAc–hexane, and the desired material was eluted with the same solvent system. The single fraction was concentrated and dried under high vacuum to afford the aldehyde.

Methyl 3-Formylbenzoate (12)[15,16]

White solid; yield: 86%.

^{1}H NMR (DMSO-d_6, 300 MHz): δ = 3.90 (s, 3 H, CO_2CH_3), 7.74 (dd, *J* = 7.5, 7.7 Hz, 1 H_{arom}), 8.14 (ddd, *J* = 1.6, 1.9, 7.5 Hz, 1 H_{arom}), 8.22 (ddd, *J* = 1.5, 1.6, 7.7 Hz, 1 H_{arom}), 8.42 (dd, *J* = 1.5, 1.9 Hz, 1 H_{arom}), 10.06 (s, 1 H, CHO).

GC-MS/EI: *m*/*z* = 164 (M^+).

3-Nitrobenzaldehyde (18)[16–19]

Pale-yellow crystals; yield: 87%.

^{1}H NMR (DMSO-d_6, 300 MHz): δ= 7.90 (dd, *J* = 7.9, 8.3 Hz, 1 H_{arom}), 8.33 (ddd, *J* = 1.2, 1.6, 7.9 Hz, 1 H_{arom}), 8.52 (ddd, *J* = 1.2, 2.2, 8.3 Hz, 1 H_{arom}), 8.68 (dd, *J* = 1.6, 2.2 Hz, 1 H_{arom}), 10.14 (s, 1 H, CHO).

GC-MS/EI: *m*/*z* = 151 (M^+).

3-Methoxybenzaldehyde (23)[16,18,21]

Colorless oil; yield: 68%.

^{1}H NMR (DMSO-d_6, 400 MHz): δ = 3.82 (s, 3 H, OCH_3), 7.26 (ddd, *J* = 2.6, 2.7, 7.1 Hz, 1 H_{arom}), 7.40 (m, 1 H_{arom}), 7.49 (m, 2 H_{arom}).

GC-MS/EI: *m*/*z* = 136 (M^+).

2-Fluorobenzaldehyde (28)[13,19,24]

Colorless liquid; yield: 81%.

^{1}H NMR (DMSO-d_6, 300 MHz): δ = 7.40 (m, 2 H_{arom}), 7.76 (m, 1 H_{arom}), 7.85 (ddd, *J* = 2.0, 7.3, 7.9 Hz, 1 H_{arom}), 10.23 (s, 1 H, CHO).

GC-MS/EI or HPLC-MS/ES: inconclusive.

Methyl 2-(Dimethylamino)-5-formylbenzoate (16)

A solution of **13** (2.85 g, 16.95 mmol) in CCl_4 (85 mL) was treated with *N*-bromosuccinimide (6.60 g, 37.08 mmol) and benzoyl peroxide (0.454 g, 1.87 mmol). The contents were refluxed for 10 h under argon, cooled to r.t. and filtered to remove succinimide. The filtrate was concentrated to a clear, yellow liquid (a mixture of **14** and **15**) that was added to aq 40% dimethylamine (80 mL). The contents were slowly heated to 56 °C for 15 min, and the heat was then removed. The dark orange solution was poured into CH_2Cl_2 (150 mL) and the layers were separated. The organic layer was concentrated to a dark yellow oil that was placed onto a column of silica gel (300 cc) equilibrated in hexane. The desired product was eluted with a gradient ranging from 20–65% EtOAc–hexane to provide **16** (2.46 g, 70%) as a clear, yellow liquid.

^{1}H NMR (DMSO-d_6, 300 MHz): δ = 2.93 [s, 6 H, $N(CH_3)_2$], 3.83 (s, 3 H, CO_2CH_3), 7.05 (d, *J* = 8.9 Hz, 1 H_{arom}), 7.79 (dd, *J* = 2.3, 8.9 Hz, 1 H_{arom}), 8.00 (d, *J* = 2.3 Hz, 1 H_{arom}), 9.73 (s, 1 H, CHO).

HPLC-MS/ES: *m*/*z* = 208 (M + 1).

Anal. Calcd for $C_{11}H_{13}NO_3$: C, 63.76; H, 6.32; N, 6.76. Found: C, 63.46; H, 6.40; N, 6.50.

4-Fluorobenzaldehyde (20)[13,15,20] and 4-Fluorobenzoic Acid (20a)[19]

A suspension of **19** (0.200 g, 0.746 mmol) in 40% aq dimethylamine (4 mL) was heated to 60 °C under argon for 10 min. The contents were then poured into CH_2Cl_2 (25 mL) and the layers were separated. The organic layer was dried (Na_2SO_4) and concentrated. The resultant liquid was placed onto a pad of silica gel (20 *cc*) equilibrated in hexane, and the desired material was eluted with 20% hexane–CH_2Cl_2. The single fraction was concentrated to afford **20** (0.080 g, 86%) as a colorless liquid.

^{1}H NMR (DMSO-d_6, 400 MHz): δ = 7.42 (m, 2 H_{arom}), 7.97 (m, 2 H_{arom}), 9.94 (s, 1 H, OH).

GC-MS/EI: *m*/*z* = 124 (M^+).

Upon standing, the liquid auto-oxidized to afford **20a** as a white crystalline solid.

^{1}H NMR (DMSO-d_6, 400 MHz): δ = 7.30 (m, 2 H_{arom}), 7.97 (m, 2 H_{arom}), 13.02 (s, 1 H, CO_2H).

GC-MS/EI: *m*/*z* = 140 (M^+).

4-(Dimethylamino)benzaldehyde (21)[28,29]

A suspension of **19** (1.0 g, 3.73 mmol) in 40% aq dimethylamine (20 mL) was heated to 60 °C under argon for 2 h. At that time, TLC (silica gel 60, CH_2Cl_2, UV detection) analysis indicated complete reaction. The contents were cooled to r.t., poured into CH_2Cl_2 (100 mL) and brine (50 mL), and the layers were separated. The organic layer was washed with brine (50 mL) and concentrated to a dark yellow oil. The residue was placed onto a column of silica gel (150 cc) equilibrated in 30% CH_2Cl_2–hexane, and the desired material was eluted with a gradient ranging from 40% CH_2Cl_2–hexane to 100% CH_2Cl_2. The single fraction was concentrated and then vacuum dried at r.t. for 30 min to afford **21** (0.457 g, 82%) as a yellow solid.

^{1}H NMR (DMSO-d_6, 300 MHz): δ = 3.03 [s, 6 H, $N(CH_3)_2$], 6.78, 7.68 (AA′BB′ quartet, J = 8.8 Hz, 4 H_{arom}), 9.65 (s, 1 H, CHO).

HPLC-MS/ES: m/z = 150 (M + 1).

3-Fluorobenzaldehyde (26)[22,23] and 3-Fluorobenzoic Acid (26a)[31]

A suspension of **25** (3.0 g, 16.76 mmol) in 40% aq dimethylamine (60 mL) was heated to 60 °C under argon for 60 min. The contents were cooled to r.t., poured into CH_2Cl_2 (50 mL) and the layers were separated. The organic layer was dried (Na_2SO_4) and concentrated to ca. 5 mL. The yellow liquid was placed onto a pad of silica gel (60 cc) equilibrated in hexane, and desired material was eluted with 10% hexane–CH_2Cl_2. The single fraction was concentrated to afford **26** (1.67 g, 80%) as a pale yellow liquid.

^{1}H NMR (DMSO-d_6, 400 MHz): δ = 7.55 (m, 1 H_{arom}), 7.65 (m, 2 H_{arom}), 7.76 (ddd, J = 1.2, 2.6, 6.3 Hz, 1 H_{arom}), 9.97 (s, 1 H, CHO).

GC-MS/EI: m/z = 124 (M^+).

After several days, the pale yellow liquid partially solidified to a white, waxy substance. This material was recrystallized from hot hexane to give **26a** (1.11 g, 59%) as white crystals.

^{1}H NMR (DMSO-d_6, 400 MHz): δ = 7.46 (m, 1 H_{arom}), 7.53 (m, 1 H_{arom}), 7.63 (m, 1 H_{arom}), 7.76 (ddd, J = 1.2, 2.4, 6.4 Hz, 1 H_{arom}), 13.26 (s, 1 H, CO_2H).

GC-MS/EI: m/z = 140 (M^+).

2-(Dimethylamino)benzaldehyde (29)[25,26]

A suspension of **27 (**2.0 g, 11.17 mmol) in 40% aq dimethylamine (40 mL) was heated to 60 °C under argon for 8 h. The yellow solution was cooled to r.t. and poured into CH_2Cl_2 (200 mL). The layers were separated and the organic layer was washed with brine (50 mL) and concentrated to a yellow liquid. The liquid was filtered through a plug of silica gel (200 cc) equilibrated in 50% CH_2Cl_2–hexane, and the desired product was eluted with CH_2Cl_2. The single fraction (ca. 300 mL) was rotary-evaporated and further concentrated under a brisk stream of argon to give **29** (1.57 g, 94%) as a yellow liquid.

^{1}H NMR (DMSO-d_6, 300 MHz): δ = 2.86 [s, 6 H, $N(CH_3)_2$], 6.99 (m, 1 H_{arom}), 7.11 (dd, J = 1.0, 8.7 Hz, 1 H_{arom}), 7.51 (ddd, J = 1.7, 7.0, 8.7 Hz, 1 H_{arom}), 7.66 (dd, J = 1.7, 7.6 Hz, 1 H_{arom}), 10.11 (s, 1 H, CHO).

2-(4-Fluorophenyl)-1,3-dimethylimidazolidine (31)

A solution of 4-fluorobenzal chloride (**24**; 0.500 g, 2.79 mmol) in *N*,*N*′-dimethylethylenediamine (2 mL) was heated to 70 °C for 14 h under N_2. At that time, the yellow solution was cooled to r.t. and poured into CH_2Cl_2 (25 mL) and H_2O (40 mL). The layers were separated and the organic layer was again washed with brine (2 × 20 mL), dried (Na_2SO_4) and concentrated to afford **31** (0.508 g, 94%) as a yellow oil.

^{1}H NMR (DMSO-d_6, 400 MHz): δ = 2.02 (s, 6 H, NCH_3), 2.48 (m, 2 H, CH_2), 3.22 (m, 2 H, CH_2), 3.22 (s, 1 H, CH), 7.13, 7.38 (AA′BB′ quartet, coupled by fluorine; 4 H_{arom}).

Anal. Calcd for $C_{11}H_{15}N_2F·0.15\ H_2O$: C, 67.08; H, 7.83; N, 14.22. Found: C, 67.18; H, 8.21; N, 14.39.

GC-MS/EI: m/z = 194 (M^+).

Acknowledgments

I would like to thank Anthony Paiva, Erin Crum and Tim He for mass spectral support, and Laszlo Musza for NMR data that led to the structural elucidation of reactive intermediates **30** and **31**.

References

(1) Salomaa, P. In *The Chemistry of the Carbonyl Group*, Vol. 1; Patai, S., Ed.; Wiley: New York, **1966**, 177–210.
(2) See, for example: (a) Omura, K.; Swern, D. *Tetrahedron* **1978**, *34*, 1651. (b) Omura, K.; Sharma, A.; Swern, D. *J. Org. Chem.* **1976**, *41*, 957. (c) Huang, S.; Omura, K.; Swern, D. *J. Org. Chem.* **1976**, *41*, 3329. (d) Marx, M.; Tidwell, T. *J. Org. Chem.* **1984**, *49*, 788. (e) Epstein, W.; Sweat, W. *Chem. Rev.* **1967**, *67*, 247. (f) Albright, J.; Goldman, L. *J. Am. Chem. Soc.* **1965**, *87*, 4214. (g) Albright, J.; Goldman, L. *J. Am. Chem. Soc.* **1967**, *89*, 2416. (h) Parikh, J.; Doering, W. *J. Am. Chem. Soc.* **1967**, *89*, 5505. (i) Corey, E.; Kim, C. *J. Am. Chem.Soc.* **1972**, *94*, 7586.
(3) See, for example: (a) Blum, J.; Pri-Bar, I. *J. Mol. Catal.* **1986**, *37*, 359. (b) Geng, L.; Lu, X. *J. Organometal. Chem.* **1989**, *376*, 41. (c) Kim, S.; Lee, S. *Bull. Korean Chem. Soc.* **1990**, *11*, 574. (d) Firouzabadi, H.; Zeynizadeh, B. *Bull. Chem. Soc. Jpn.* **1997**, *70*, 155. (e) Cha, J.; Kim, J.; Chun, J.; Kwon, O.; Kwon, S.; Han, S. *Org. Prep. Proced. Int.* **1999**, *31*, 204.
(4) Fuson, R. In *The Chemistry of the Carbonyl Group*, Vol. 1; Patai, S., Ed.; Wiley: New York, **1966**, 211–232.
(5) Xi, F.; Kamal, F.; Schenerman, M. *Tetrahedron Lett.* **2002**, *43*, 1395.
(6) Nace, H.; Monagle, J. *J. Org. Chem.* **1959**, *24*, 1792.
(7) Kornblum, N.; Jones, W.; Anderson, G.; Jones, A. *J. Am. Chem. Soc.* **1959**, *81*, 4113.
(8) Baik, W.; Lee, H.; Jang, J.; Koo, S.; Kim, B. *J. Org. Chem.* **2000**, *65*, 108.
(9) Angyal, S. *Org. React.* **1954**, *8*, 197.
(10) Abou-Teim, O.; Jansen, R.; McOmie, J.; Perry, D. *J. Chem. Soc., Perkin Trans. 1* **1980**, 1841.
(11) *Note*: These reactions were conducted at temperatures below 70 °C, which are not high enough to promote significant decomposition of DMF. Decomposition of DMF became relevant at temperatures around 140 °C.
(12) Nagayama, K.; Shimizu, I.; Yamamoto, A. *Chem. Lett.* **1998**, 1143.
(13) Laali, K.; Herbert, M.; Cushnyr, B.; Bhatt, A.; Terrano, D. *J. Chem. Soc., Perkin Trans. 1* **2001**, 578.
(14) Miyabe, H.; Torieda, M.; Kiguchi, T.; Naito, T. *Synlett* **1997**, 580.
(15) Baillargeon, V.; Stille, J. *J. Am. Chem. Soc.* **1986**, *108*, 452.
(16) Goswami, S.; Mahapatra, A. *Tetrahedron Lett.* **1998**, *39*, 1981.
(17) Li, C.; Xu, Y.; Lu, M.; Zhao, Z.; Liu, L.; Zhao, Z.; Cui, Y.; Zheng, P.; Ji, X.; Gao, G. *Synlett* **2002**, 2041.
(18) Hajipour, A.; Mallakpour, S.; Baltork, I.; Backnezhad, H. *Synth. Commun.* **2002**, *32*, 771.
(19) Corriu, R.; Lanneau, G.; Perrot, M. *Tetrahedron Lett.* **1987**, *28*, 3941.
(20) Russ, R.; Zelinski, T.; Anke, T. *Tetrahedron Lett.* **2002**, *43*, 791.
(21) Shawcross, A.; Stanforth, S. *Tetrahedron* **1989**, *45*, 7063.

(22) Krohn, K.; Khanbabaee, K.; Rieger, H. *Chem. Ber.* **1990**, *123*, 1357.
(23) Centi, G.; Perathoner, S. *Top. Catal.* **2001**, *15*, 145.
(24) Milner, D. *Synth. Commun.* **1992**, *22*, 73.
(25) Kienzle, F. *Tetrahedron Lett.* **1983**, *24*, 2213.
(26) Gupton, J.; Idoux, J.; Baker, G.; Colon, C.; Crews, A.; Jurss, C.; Rampi, R. *J. Org. Chem.* **1983**, *48*, 2933.
(27) Pfoertner, K.; Bernauer, K.; Kaufman, F.; Lorch, E. *Helv. Chim. Acta* **1985**, *68*, 584.
(28) Downie, I.; Earle, M.; Heaney, H.; Shuhaibar, K. *Tetrahedron* **1993**, *49*, 4015.
(29) Ganguly, N.; Sukai, A.; De, S.; De, P. *Synth. Commun.* **2001**, *31*, 1607.
(30) Cecchetto, A.; Minisci, F.; Recupero, F.; Fontana, F.; Pedulli, G. *Tetrahedron Lett.* **2002**, *43*, 3605.
(31) Laev, S.; Shteingarts, V. *Tetrahedron Lett.* **1995**, *36*, 4655.