Synthesis of *N*-formylmaleamic acid and some related *N*-formylamides

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Two syntheses of *N*-formylmaleamic acid and some related *N*-formylamides are described which take place under very mild conditions.

Keywords: *N*-formylmaleamic acid, *N*-formylamides, formamidine, periodate

A number of routes to *N*-formylamides have been described[1-19] but none seemed suitable for *N*-formylmaleamic acid both because of its exceptional lability[20] and because of separation problems from starting materials. The difficulties are: (a) the formyl group is rather easily hydrolysed under both acidic and basic conditions;[20] (b) strong oxidants must be avoided because of the olefinic-bond; (c) high temperatures result in isomerisation to the *trans*-isomer, *N*-formylfumaramic acid.[20] Also conventional acid chlorides of formic and maleic acids are not available. The acid–base lability of *N*-formylamides is a general property.[14] We report here two syntheses of *N*-formylamides which both have the advantage of very mild conditions. The first is the reaction discovered by Hillenbrand[21,22] in which an acid anhydride (or acid halide) reacts with formamidine acetate to yield, initially, an amidine (Fig. 1). The amidine undergoes ready hydrolysis to give the *N*-formyl compound. (A related synthesis[6] using dimethylformamidinium salts failed in this case in our hands.) Using this procedure, we report the synthesis of *N*-formylmaleamic acid, *N*-formylbenzamide, 4-chloro-*N*-formylbenzamide, and *N*-formylphthalamic acid. The principal drawback of this route is the low yield and separation problems due to the alternative cleavage of the tetrahedral intermediate which leads to formamide and the amide of the parent acid.[23,24] Formamide does not arise from hydrolysis of formamidine itself as this process has a half-life of days. It is worth noting that in the synthesis of *N*-formylphthalamic acid, phthalimide is slowly formed; it can be removed by extraction with ethyl acetate. (Phthalimide's proton NMR spectrum shows, remarkably, a singlet at δ 7.82 for both types of aromatic protons.) In the case of *N*-formylmaleamic acid, the product of the alternative cleavage is maleamic acid and the separation from the *N*-formyl compound could only be achieved by column chromatography.[21] The second synthesis of *N*-formylmaleamic acid reported here is by condensation of maleamic acid with phenylglyoxal followed by periodate cleavage of the product (Fig. 2). The phenyl group provides a crystallisation handle which makes isolation of the intermediate (and separation from starting materials) convenient.

There are two previous syntheses of *N*-formylmaleamic acid, one by ozonolyis of 2-pyridone where the molecule was detected as a transient[25] and the other by photoisomerisation of the *trans*-isomer, *N*-formylfumaramic acid.[20] *N*-Formylfumaramic acid has been made by reaction of formamide with maleic anhydride and well-characterised.[20,26] In contrast to the *cis*-isomer, it has, *inter alia*, low solubility in water, the highest carbonyl absorption at 1737 cm^{-1}, *J* values for its olefinic protons of 16.5 Hz, and about double the extinction coefficient at 225 nm. Our particular interest in *N*-formylmaleamic acid stems from the fact that it is an intermediate in the bacterial oxidation of nicotinic acid.[20] Hillenbrand[21] showed that *N*-formylmaleamic acid was rapidly hydrolysed by bacterial extracts to maleamic and formic acids under conditions where *N*-formylfumaramic acid is not attacked.

Experimental

Instrumentation: UV, Shimadzu Bio-mini with a resolution of about 2 nm; IR, Nicolet Impact 410 single beam instrument; NMR, various Bruker instruments.

N-Formylphthalamic acid (with Cupler, Yahner, and El-Khoury)
Formamidine acetate (1.04 g, 0.01 mol), purified by washing with ethanol to remove ammonium acetate, was dissolved in 2 ml water. Acetone (13 ml) was added and then 1.5 g (0.01 mol) of freshly fused phthalic anhydride. The mixture was stirred at room temperature until a homogeneous solution formed (about 15 min). The acetone was removed by rotary evaporation at room temperature (water pump). Cold water (10 ml) was added to the resulting syrup followed by 0.08 ml of conc. HCl (0.01 mol). Crystallisation was allowed to proceed overnight at 5°C. The solid mass was filtered and washed with cold water. Air drying at room temperature gave 1 g (52%) of

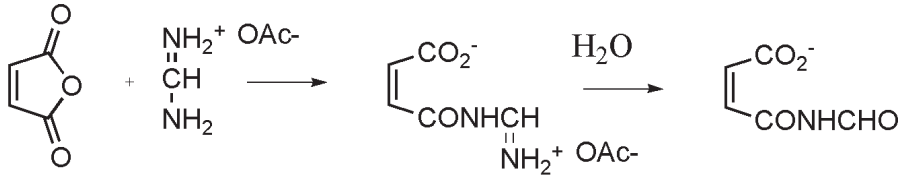

Fig. 1 Synthesis of *N*-formylmaleamic acid by reaction of maliec anhydride and formamidine acetate.

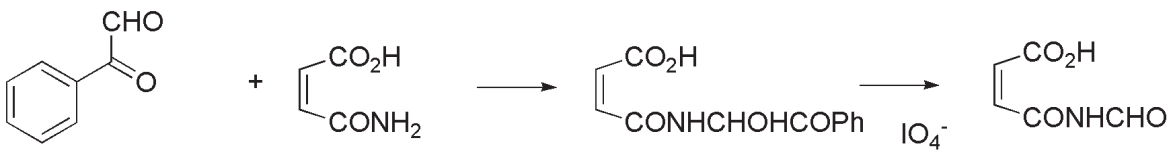

Fig. 2 Synthesis of *N*-formylmaleamic acid from phenylglyoxal and maleamic acid.

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the crude product. Recrystallisation from 50% ethanol yielded a pure product, m.p. 158–159°C (lit.[5] 150–151°C). Anal.: calcd for $C_9H_7NO_4$: C, 55.96; H, 3.65; N, 7.25. Found: C, 56.06; H, 3.64; N, 7.11. MS: calcd. 193.0373, found 193.0372. [When the reaction was carried out in O-18 labelled water and analysed by (+)SIMS, the product showed an MH^+ ion at *m/e* 198 indicating the presence of two O-18 atoms.] UV: λ_{max}, ε: 276 nm, 1400 $M^{-1}cm^{-1}$ (95% ethanol). ^{1}H NMR, 500 MHz, DMSO-d_6: δ 7.53 (1H, dd, J_m = 0.8 Hz, J_o = 7.1 Hz), 7.61 (1H, ddd, J_m = 1.4 Hz, J_o = 7.6 Hz), 7.67 (1H, ddd, J_m = 1.4 Hz, J_o = 7.5 Hz), 7.91 (1H, dd, J_m = 1.0 Hz, J_o = 7.0 Hz), 9.04 (1H, br), 11.53 (1H, d, 9.2 Hz), 13.3 (1H, br). ^{13}C NMR,125.7 MHz, DMSO-d_6:δ 127.6, 129.6, 129.7, 130.4, 132.1, 136.2, 163.5, 166.9, 170.6.. IR: Nujol and Fluorolube mulls: 3400, 3288, 3206, 2920, 2675, 2553, 1725, 1680, 1487, 1246, 1193, 713 cm^{-1}. The ammonium salt was crystallised from propan-1-ol, m.p. 142–143°C. Anal: calcd. for $C_9H_{10}N_2O_4$: C, 51.43; H, 4.79; N, 13.33. Found: C, 5l.63; H, 4.93; N, 13.16. ^{13}C NMR, δ 125.7 MHz, DMSO-d_6: 128.1, 129.4, 130.7, 132.6, 133.3, 138.6, 166.8, 174.0, 175.7.

N-Formylbenzamide (with Dong): Formamidine acetate (2.1 g, 0.02 mol) was dissolved in 4 ml water. Acetone (26 ml) was added and then sodium bicarbonate (1.7 g, 0.02 mol). The two-phase mixture was stirred on ice while 2.3 ml (0.02 mol) benzoyl chloride was added dropwise during 10 min. An initial flocculent precipitate was gradually replaced by a granular one. This precipitate was removed by filtration after one hour. Most of the acetone was removed by rotary evaporation. The residue was partitioned between methylene chloride and dilute sodium bicarbonate to remove benzoate. The methylene chloride layer was washed with water, dried with magnesium sulfate, and evaporated to yield 0.6 g (20%) of crude material. Crystallisation from 100 ml hexane gave 0.3 g of fine needles, m.p. 100–110°C. A second crystallisation from 60 ml hexane gave pure material which sintered at 100°C and melted at 105–108°C (lit.[4,6,17] 106–108°C, 112–113°C, 111–113°C). MS: calcd. 149.0475, found 149.0477. ^{1}H NMR, 500 MHz, $CDCl_3$: δ 7.55 (2H, ddd, *J* = 8.6, 1.3 Hz), 7.66(1H, ddd, *J* = 8.7, 1.3 Hz), 7.94 (2H, dd, *J* = 7, 1.3 Hz), 9.4(2H, br). IR: Nujol mull: 3272, 1725, 1686, 1672, 1251, 1157, 1061, 885, 701 cm^{-1}.

4-Chloro-N-formylbenzamide (with Zechinati): Formamidine acetate, 2.1 g (0.02 mol) and sodium bicarbonate, 2 g(0.024 mol) were added to a solution of 4-chlorobenzoyl chloride (3.5 g, 0.02 mol) in 30 ml methylene chloride. The mixture was stirred for 20 h at room temperature with the exclusion of moisture. The solvent was removed by rotary evaporation. Acetone (30 ml) was added together with additional formamidine acetate (1.1 g) and sodium bicarbonate (1 g). After stirring for 1 h, the acetone was removed and the residue dissolved in ethyl acetate. The solution was washed with dilute sodium bicarbonate, water, and dried with magnesium sulfate. Rotary evaporation yielded 2.0–2.35 g (54–64%) of crude product. Trituration with ethanol removed a 4-chlorobenzamide impurity. Recrystallisation from toluene gave a pure product, m.p. 191–194°C (lit.[27] 95–96°C, which may be a misprint as the nmr data are misassigned). Anal. Calcd. for $C_8H_6O_2NCl$: C, 52.33; H, 3.09; N, 7.63. Found: C, 52.40; H, 3.09; N, 7.51. ^{1}H NMR, 600 MHz, $CDCl_3$: δ 7.53 (2H, d, *J* = 8.4 Hz), 7.90 (2H, d, *J* = 8.4 Hz), 9.37 (1H, d, *J* = 9.6 Hz), 9.55 (1H, s). IR, Nujol: 3263, 1738, 1693, 1593, 1255, 1222, 1091, 1066, 849, 748 cm^{-1}.

N-Formylmaleamic acid; (a) By reaction of maleic anhydride and formamidine acetate:[21]
Formamidine acetate (1.0 g, 0.01 mol) was added to 50 ml of acetone containing 4% water. Maleic anhydride (0.01 mol) was added with stirring to yield a clear solution. After 10 min, the acetone and water were removed by rotary evaporation and then the acetic acid was removed with an oil pump. This yields about 0.6 g of a white solid which, by NMR analysis, contains 30–40% of N-formylmaleamic acid together with maleic and maleamic acids in smaller amounts. The only method of purification found was ion-exchange column chromatography. An AG-l-X4 column in the chloride form using a KCl eluant resolved the three components at pH 4. Maleamic acid elutes first followed by *N*-formylmaleamic acid and finally maleic acid. Water was removed from the column eluates by rotary evaporation. *N*-formylmaleamic acid was then extracted by ethanol. Alternatively, if LiCl was used as the eluant, Sephadex could be used to separate the salt from the product. Spectroscopic data follow the description of the alternate synthesis of *N*-formylmaleamic acid below.

(b) By reaction of maleamic acid and phenylglyoxal: Maleamic acid (1.15 g, 0.01 mol) and phenylglyoxal (1.52 g, 0.01 mol) were dissolved in 10 ml DMSO. Then 1.4 g (0.01 mol) potassium carbonate was added and the mixture stirred at RT overnight. The orange reaction mixture was diluted with 500 ml ethyl acetate and kept at 5°C overnight. The ethyl acetate was decanted from the precipitated oil, the oil washed with fresh ethyl acetate several times, and finally with ether. The dried residue was then taken up in 30 ml cold water. Conc. HCl, 1.5 ml, was slowly added with stirring. This gives an opalescent supernatant layer and a brown sticky precipitate. The opalescent material was decanted from the brown material and allowed to crystallise for a few hours at 5°C. The crude product was filtered and washed with cold water. The yield was about 1.5 g (60%). The product, *N*-(1-hydroxy-2-oxo-2-phenylethyl)maleamic acid (NHOPM), was purified by crystallisation from chloroform. M.p. 110–111°C. Anal.: calc. for $C_{12}H_{11}NO_5.1/4H_2O$; C, 56.80; H, 4.57; N, 5.52. Found: C, 56.70; H, 4.21; N, 5.49. MS: calcd for M + Na, 272.056, found, 272.052. ^{1}H NMR, 600 MHz, DMSO-d_6: δ 6.32 (1H, d, *J* = 12.2 Hz), 6.36(1H, d, *J* = 12.2 Hz), 6.41 (1H, dd, *J* = 7.3 Hz), 6.89 (1H, d, *J* = 7.1 Hz), 7.55 (2H, dd, *J* = 7.7 Hz), 7.67 (1H, dd, *J* = 7.3 Hz), 8.00 (2H, d, *J* = 7.3 Hz), 9.47(1H, d, *J* = 8.3 Hz), 13.5(1H, br). IR: Nujol: 3388, 3323, 3238, 1699, 1627, 1532, 1282, 1259, 1219, 1104, 1095, 1070, 1059, 992, 977, 855, 836, 762, 707 cm^{-1}.

Oxidation of NHOPM with periodate: NHOPM (125 mg, 0.5 mmol) was added to a solution of 150 mg $NaIO_4$(0.7 mmol) in 5 ml water at 5°C. Sodium bicarbonate (42 mg, 0.5 mmol) was added with stirring. The pH should be about 4. A precipitate of benzoic acid forms gradually. After 1 h, 2 drops of 1M sulfuric acid were added and the benzoic acid filtered on a Büchner. The cold solution was then extracted three times with ether to remove any remaining benzoic acid. The pH of the solution was readjusted to pH 4 with solid sodium bicarbonate and then taken to dryness on a rotary evaporator at 30°. The sodium salt of *N*-formylmaleamic acid was extracted from the residue of sodium iodate by trituration with methanol. Removal of the methanol by rotary evaporation yielded the sodium salt of *N*-formylmaleamic acid contaminated with a little sodium iodate.[28] The material was purified by extraction with ethanol (in which sodium iodate is less soluble) followed by drying *in vacuo* (oil pump). The yield was 60–70%. Anal.: calcd. for $C_5H_4NO_4Na.0.5H_2O$ with 1.35% $NaIO_3$: C, 33.95; H, 2.83; N, 7.92. Found: C, 34.02; H, 3.19; N, 7.45. This quantity of sodium iodate was confirmed by iodometric titration. (Note that iodate and periodate may be distinguished by the pH-dependencies of their reactions with iodide.[29])

MS.: Calcd.for M + H 166.012, found 166.006. UV(water): (λ_{max}, nm; ε, $M^{-1}cm^{-1}$;)227, 10,500. For comparative purposes(sodium salts in water): *N*-formylfumaramic acid:225, 20,600; maleamic acid: 201, 10,000; fumaramic acid: 210, 18,950. ^{1}H NMR, 600 MHz, DMSO-d_6: δ 5.69 (1H, d, *J* = 13.2 Hz), 6.34 (1H, dd, *J* = 13.3, 1.1 Hz) (the four bond coupling establishes this resonance as H-3), 9.05 (1H, d, *J* = 8.9 Hz), 16.3(1H, br.). D_2O: δ 5.98 (1H, d, *J* = 12.2 Hz), 6.58 (1H, d, *J* = 12.2 Hz), 8.98 (1H, s). ^{13}C NMR, 150.9 MHz, DMSO-d_6(doublets using gated decoupling):δ 126.9 (*J* = 161 Hz), 144.2 (*J*=156 Hz), 164.2 (*J*=202 Hz), 167.2 (*J*=14.4 Hz), 167.6 (*J*=11.6 Hz). IR, Nujol: 1719, 1680, 1588, 1548, 1531, 1353, 1232, 862 cm^{-1}.

We are grateful to E. Cupler, S. El-Khoury, A. Yahner, S. Buchholz, B. Zechinati, and Y. Dong for many contributions. We also thank Dr. C. E. Cottrell for suggesting the gated decoupling experiment.

Received 16 February 2008; accepted 17 March 2008
Paper 08/5098 doi: 10.3184/030823408X304005

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