Supplementary Material for Organic & Biomolecular Chemistry

Supplementary Information

Concise Routes to Pyrazolo[1,5-*a*]pyridin-3-yl Pyridazin-3-ones

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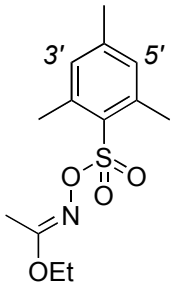
N-Aminopyridinium Mesitylenesulfonate

N-Aminopyridinium mesitylenesulfonate was prepared by adaptation of the procedure reported by Tamura *et al* through amination of pyridine with *O*-mesitylenesulfonylhydroxylamine (MSH).[1] **CAUTION: MSH is explosively unstable as a dry solid.** To minimise the explosion hazard we isolated MSH as a water-wet solid. The solid was immediately dissolved in dichloromethane and then dried and used in solution form for subsequent reactions. Quantification was possible by evaporating an aliquot of MSH solution and then weighing the resulting dry powder (100-200 mg quantities).

Ethyl N-mesitylsulfonyloxyethanimidate (MSA)



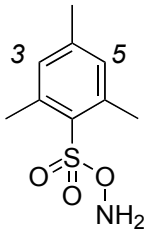
$C_{13}H_{19}NO_4S$
285.36

To an ice-cooled solution of ethyl *N*-hydroxyacetimidate (7.45 g, 72.2 mmol) in anhydrous DMF (30 mL) was added triethylamine (11.0 mL, 78.9 mmol) followed after 15 min by mesitylenesulfonyl chloride (15.9 g, 72.7 mmol) in increments over 15 min. The solution was allowed to attain room temperature over 1 h. The resulting slurry was poured into ice-cold water (200 mL) and the precipitate collected by filtration. The filter cake was washed with cold water (200 mL) and dried *in vacuo* to afford the *title compound* (18.5 g, 64.8 mmol; 90%) as a colourless powder: ν_{max}(KBr)/cm^{-1} 2982, 2941, 1636, 1605, 1383, 1318, 1195, 1101, 1055, 963, 851, 814, 668; δ_H (200 MHz; $CDCl_3$) 1.18 (3 H, t, *J* 7.1, C**H**$_3$CH$_2$O), 2.04 (3 H, s, C(C**H**$_3$)OEt), 2.31 (3 H, s, 4'-CH_3), 2.64 (6 H, s, 2'-CH_3 & 6'-CH_3), 3.90 (2 H, q, *J* 7.1, CH_3C**H**$_2$O), 6.96 (2 H, s, H-3' & H-5'); δ_C (50 MHz; $CDCl_3$)[2] 14.1 (**C**H$_3$CH$_2$O), 15.0 (**C**H$_3$C=N), 21.2 (4'-CH_3), 23.0 (2'-CH_3 & 6'-CH_3), 63.7 (CH_3**C**H$_2$O), 130.5 (C-4'), 131.6 (CH-3' & CH-5'), 140.8 (C-2' & C-6'), 143.4 (C-1'), 169.3 (C=N); (Found: C, 54.80; H, 6.79; N, 4.92. Calculated for $C_{13}H_{19}NO_4S$: C, 54.72; H, 6.71; N, 4.91%).

(1) (a) Y. Tamura, J. Minamikawa and M. Ikeda, *Synthesis*, **1977**, 1; (b) Y. Tamura, J. Minamikawa, K. Sumoto, S. Fujii and M. Ikeda, *J. Org. Chem.*, **1973**, *38*, 1239; (c) Y. Tamura, J. Minamikawa, Y. Miki, S. Matsugashita and M. Ikeda, *Tetrahedron Lett.*, **1972**, *13*, 4133.

(2) ^{13}C NMR assignments for compound MSA were supported by the acquisition of an HSQC spectrum.

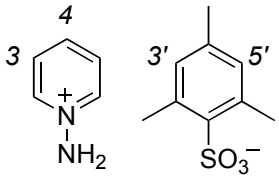
O-Mesitylenesulfonylhydroxylamine (MSH)



$C_9H_{13}NSO_3$
215.27

An ice-cooled, briskly stirred solution of ethyl *N*-mesitylsulfonyloxyethanimidate (27.3 g, 95.5 mmol) in 1,4-dioxane (55 mL) was treated dropwise over 8 min with perchloric acid (70% w/w; 48.8 g, 340 mmol). A viscous paste was formed shortly after completing the perchloric acid addition. Further dioxane (55 mL) was added to assist stirring and the mixture maintained in the ice bath for 1 h. The resulting slurry was poured into ice-cold water (600 mL) and the precipitate collected by filtration, washing with ice-cold water (500 mL). The wet filter cake was then dissolved in dichloromethane (250 mL) and the resulting solution washed with brine (100 mL), dried by filtration through a plug of $MgSO_4$ and used directly for preparation of the *N*-aminopyridinium salt. Evaporation of a small sample of MSH solution to dryness [**CAUTION**] permitted NMR analysis: δ_H (200 MHz; $CDCl_3$) 2.30 (3 H, s, 4-CH_3), 2.60 (6 H, s, 2-CH_3 & 6-CH_3), 6.78 (2 H, br s, NH_2), 6.96 (2 H, s, H-3 & H-5).

N-Aminopyridinium Mesitylenesulfonate[1]

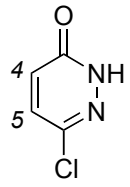


$C_{14}H_{18}N_2O_3S$
294.37

To a solution of MSH (prepared as above from MSA, 95.5 mmol) in CH_2Cl_2 (250 mL) was added pyridine (10.0 mL, 124 mmol). The mixture was stirred for 18 h at room temperature during which time the *N*-aminopyridinium salt crystallised directly from the reaction medium. The resulting slurry was diluted with hexane (250 mL); the solid was collected by filtration, washing well with Et_2O, and dried *in vacuo* over P_2O_5 to afford the *title salt* (23.0 g, 78.3 mmol; 82% over the 2 steps from MSA) as a colourless powder: mp 118-120 °C (from CH_2Cl_2-hexane); ν_{max}(KBr)/cm^{-1} 3283, 3129, 3074, 1491, 1210, 1182, 1012, 846, 772, 682; δ_H (200 MHz; DMSO-d_6) 2.16 (3 H, s, 4'-CH_3), 2.49 (6 H, s, 2'-CH_3 & 6'-CH_3), 6.75 (2 H, s, H-3' & H-5'), 7.95-8.04 (2 H, m, H-3 & H-5), 8.21-8.29 (1 H, m, H-4), 8.54 (2 H, br s, NH_2), 8.75-8.81 (2 H, m, H-2 & H-6); δ_C (50 MHz; DMSO-d_6)[3] 20.4 (4'-CH_3), 22.8 (2'-CH_3 & 6'-CH_3), 128.3 (CH-3 & CH-5), 130.0 (CH-3' & CH-5'), 136.0 (C-2' & C-6'), 136.6 (C), 138.3 (CH-2 & CH-6), 139.7 (4-CH), 142.5 (C); (Found C, 56.99; H, 6.15; N, 9.45. Calculated for $C_{14}H_{18}N_2O_3S$: C, 57.12; H, 6.16; N, 9.52%).

(3) ^{13}C NMR assignments for N-aminopyridinium mesitylenesulfonate were supported by the acquisition of an HSQC spectrum.

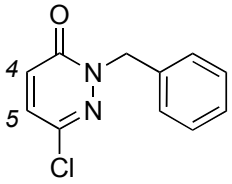
6-Chloropyridazin-3(2*H*)-one (23)[4]



$C_4H_3ClN_2O$
130.53

3,6-Dichloropyridazine (12.9 g, 86.4 mmol) was boiled in glacial AcOH (200 mL) for 3 h. The mixture was then concentrated by distillation at atmospheric pressure. After cooling, the residue was dissolved in H_2O (50 mL) and the mixture adjusted to pH 7 by addition of saturated $NaHCO_3$ solution. The resulting precipitate was collected by filtration, washed with water and dried *in vacuo* over P_2O_5 to afford 6-chloro-2*H*-pyridazin-3-one (10.7 g, 82.0 mmol; 95%) as a colourless powder: mp 142-143 °C; ν_{max}(KBr)/cm^{-1} 3208, 3055, 2918, 2849, 1673, 1582, 1545, 1289, 1143, 1114, 1005, 839, 673; δ_H (200 MHz; DMSO-d_6) 6.97 (1 H, d, *J* 9.7), 7.51 (1 H, d, *J* 10.0); δ_C (50 MHz; DMSO-d_6) 132.6 (CH), 134.8 (CH), 137.5 (C-6), 159.8 (C-3); *m/z* (EI) 130 (^{35}Cl; 96%, M^+), 102 (^{35}Cl; 81%, M^+-N_2), 95 (5%, M^+- Cl); (Found: C, 36.68; H, 2.26; N, 21.32. Calculated for $C_4H_3ClN_2O$: C, 36.81; H, 2.32; N, 21.46%).

2-Benzyl-6-chloropyridazin-3(2*H*)-one (24)[5]



$C_{11}H_9ClN_2O$
220.66

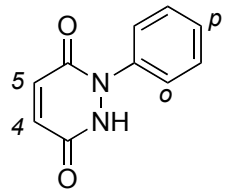
To a stirred solution of 6-chloropyridazin-3(2*H*)-one (10.5 g, 80.4 mmol) in anhydrous DMF (150 mL) under argon was added Cs_2CO_3 (45.8 g, 141 mmol) followed, after 30 minutes, by benzyl bromide (12.0 mL, 101 mmol). The heterogeneous mixture was stirred for 2.5 h at room temperature; it was then filtered and the filtrate concentrated *in vacuo* to afford an orange solid. This residue was dissolved in EtOAc (100 mL); the resulting solution washed with H_2O (30 mL) followed by brine (2 x 30 mL), dried ($MgSO_4$) and the solvent evaporated to yield a yellow solid. Recrystallisation of this material from EtOAc-petroleum 60-80 °C (1:9) yielded the *title compound* (11.7. g, 52.9 mmol; total yield 66%): mp 97-98 °C (EtOAc-petroleum); ν_{max}(KBr)/cm^{-1} 3031, 2962, 1659, 1576, 1294, 1130, 1061, 901, 840, 749, 699; δ_H (200 MHz; $CDCl_3$) 5.25 (2 H, s, C**H$_2$**Ph), 6.90 (1 H, d, *J* 9.7), 7.15 (1 H, d, *J* 9.7), **7**.28-7.47 (5 H, m, Ph); δ_C (50 MHz; $CDCl_3$) 55.6 (**C**H_2Ph), 128.3 (CH), 128.8 (2 x Ph CH), 129.0 (2 x Ph CH), 132.4 (CH), 133.8 (CH), 135.6 (C), 137.6 (C), 158.9 (C-3); *m/z* (EI) 220 (^{35}Cl; 44%, M^+), 185 (66%, M^+- Cl), 91

(4) (a) H. Feuer and H. Rubinstein, *J. Org. Chem.,* **1959**, *24*, 811; (b) W. J. Coates and A. McKillop, *Heterocycles*, **1993**, *35*, 1313; (c) A. Katrusiak and A. Katrusiak, *J. Mol. Struct.*, **2003**, *647*, 203; (d) F. Yoneda and Y. Nitta, *Chem. Pharm. Bull.*, 1963, **11**, 269.

(5) F. Yoneda and Y. Nitta, *Chem. Pharm. Bull.*, 1963, **11**, 737.

(100%, $C_7H_7^+$); (Found: C, 59.88; H, 4.10; N, 12.60. Calculated for $C_{11}H_9ClN_2O$: C, 59.88; H, 4.11; N, 12.70%).

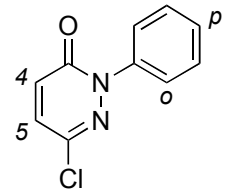
1-Phenyl-1,2-dihydropyridazine-3,6-dione (26)[6]



$C_{10}H_8N_2O_2$
188.18

A mixture of maleic anhydride (25.1 g, 256 mmol) and phenylhydrazine (27.5 mL, 280 mmol) was boiled in glacial AcOH (100 mL) for 3 h. On cooling, a yellow precipitate formed; this was collected by filtration and recrystallised from EtOH to afford the *title compound* (22.4 g, 118 mmol; 47%) as a colourless crystalline solid: mp 273-274 °C; ν_{max}(KBr)/cm^{-1} 3000, 3058, 2362, 1661 (CO), 1492, 1452, 1250, 838, 682; δ_H (200 MHz; DMSO-d_6) 7.01 (1 H, d, *J* 9.8), 7.17 (1 H, d, *J* 9.8), 7.31-7.58 (5 H, complex overlapping m, Ph), 11.35 (1 H, br s, NH); δ_C (50 MHz; DMSO-d_6) 125.6 (2 x Ph CH), 127.5 (CH), 127.7 (CH), 128.5 (2 x Ph CH), 134.0 (CH), 141.5 (Ph C), 152.9 (C), 157.8 (C); *m/z* (ESI) 188 (12%, M^+), 187 (38%, M^+- H), 375 (100%, 2M-1); (Found: C, 63.72; H, 4.20; N, 14.68. Calculated for $C_{10}H_8N_2O_2$: C, 63.82; H, 4.28; N, 14.89%).

6-Chloro-2-phenylpyridazin-3(2*H*)-one (27)[7]



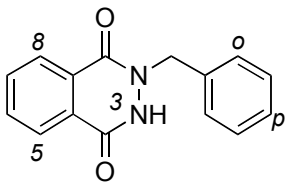
$C_{10}H_7ClN_2O$
206.63

1-Phenyl-1,2-dihydropyridazine-3,6-dione (**18**; 2.04 g, 10.8 mmol) was boiled in $POCl_3$ (55 mL) for 2 h. After this period, most of the $POCl_3$ was removed by distillation. The resulting brown residue was dissolved in EtOAc (50 mL) and washed with saturated $NaHCO_3$ solution (6 x 20 mL) until cessation of effervescence. The organic layer was further washed with brine (3 x 20 mL), dried over $MgSO_4$ and evaporated to yield a pale yellow solid. The latter was recrystallised from light petroleum to afford the *title compound* (1.71 g, 8.28 mmol; 77%) as a colourless crystalline solid: mp 115-117 °C (from light petroleum); ν_{max}(thin film)/cm^{-1} 3018, 1674, 1587, 1216, 755, 692; δ_H (200 MHz; $CDCl_3$) 7.04 (1 H, d, *J* 9.8), 7.25 (1 H, d, *J* 9.8), 7.35-7.62 (5 H, complex overlapping m, Ph); δ_C (50 MHz; $CDCl_3$) 125.3 (2 x Ph CH), 128.8 (CH), 129.0 (2 x Ph CH), 133.4 (CH), 133.8 (CH), 138.3 (C), 140.8 (C), 158.6 (C-3); *m/z* (ESI) 206 (^{35}Cl; 12%, M^+), 205 (^{35}Cl; 25%, M^+- H), 411 (^{35}Cl; 68%, 2M-1); (Found: C, 58.24; H, 3.45; N, 13.47. Calculated for $C_{10}H_7ClN_2O$: C, 58.13; H, 3.41; N, 13.56%).

(6) W. H. Pirkle and P. L. Gravel, *J. Org. Chem.,* **1977**, *42*, 1367.

(7) (a) J. Druey, A. Huni, D. H. Rinigier and A. Staehelin, *Helv. Chim. Acta.*, **1954**, *37*, 510; (b) V. P. Feshin, S. A. Giller, L. Y. Avota, M. G. Voronkov, *Chem. Heterocycl. Compd. (English Translation)*, **1976**, *12*, 334.

2-Benzyl-2,3-dihydrophthalazine-1,4-dione (31)[8]

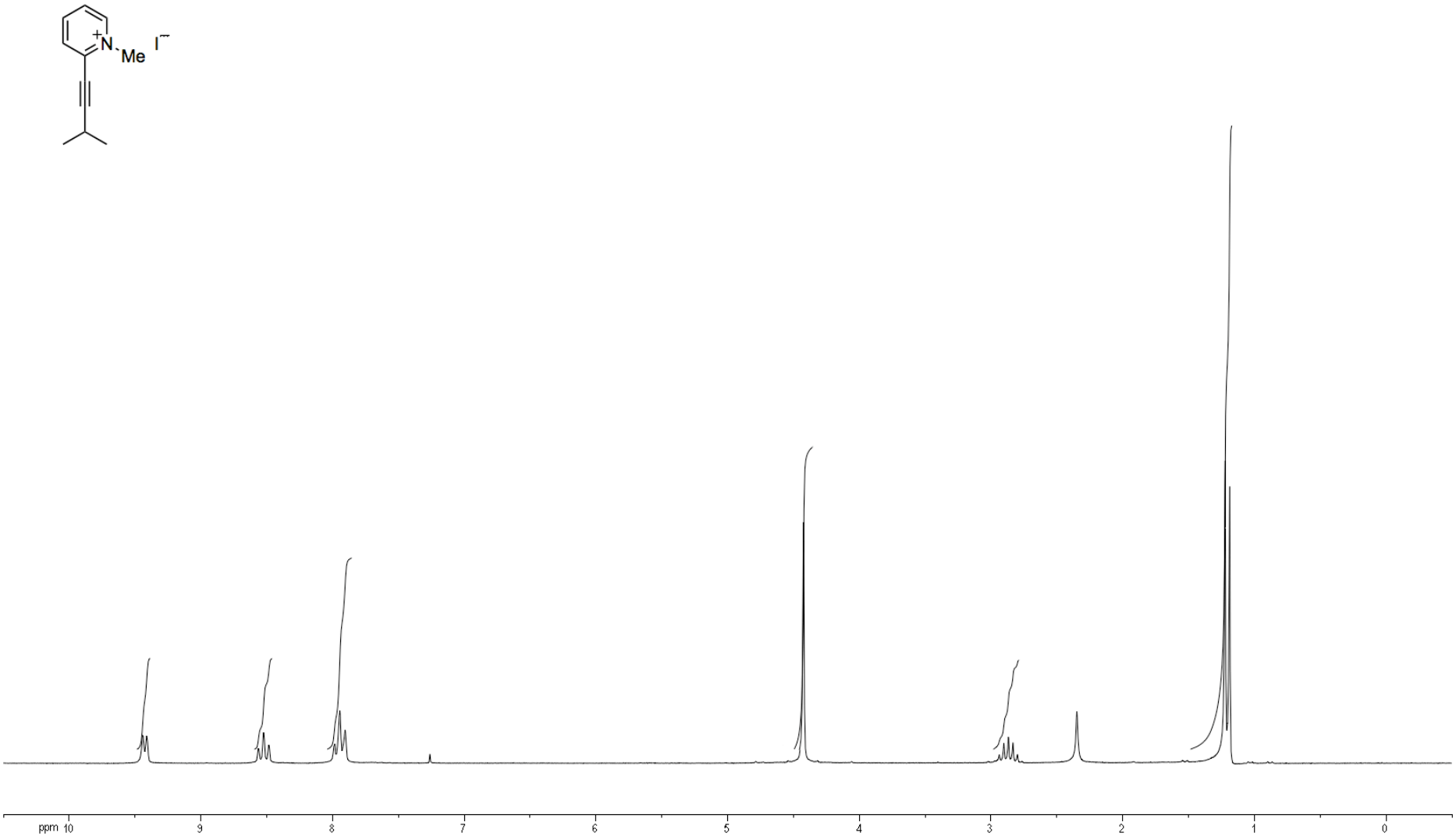


$C_{15}H_{12}N_2O_2$
252.27

Phthalic anhydride (4.19 g, 28.3 mmol) and benzylhydrazine dihydrogen chloride (5.09 g, 28.3 mmol) were boiled in glacial AcOH (100 mL) for 4 h. The mixture was evaporated and the resulting residue dissolved in EtOAc (20 mL). The solution was then washed with saturated $NaHCO_3$ solution until all residual AcOH was removed. The organic layer was further washed with brine (3 x 15 mL) and then dried (Na_2SO_4) and evaporated to give a white solid. The latter was recrystallised from MeOH/light petroleum to afford the *title compound* (4.73 g, 18.7 mmol; 66%) as a colourless powder: mp 210-211 °C (from MeOH/light petroleum); ν_{max}(KBr)/cm^{-1} 3100, 1634, 1595, 1289, 1169, 1097, 792, 744, 709, 691; δ_H (200 MHz; DMSO-*d*$_6$) 5.19 (2 H, s, C**H**$_2$Ph), 7.22-7.34 (5 H, complex overlapping m, Ph), 7.85-7.99 (3 H, complex overlapping m, 3 x CH), 8.23-8.29 (1 H, complex m, CH), 11.75 (1 H, br s, NH); δ_C (50 MHz; DMSO-*d*$_6$) 52.6 (**C**H_2Ph), 124.2 (CH), 124.7 (C), 126.6 (CH), 127.3 (CH), 127.5 (2 x CH), 128.5 (2 x CH), 128.8 (C), 132.4 (CH), 133.3 (CH), 137.6 (C), 150.4 (C), 157.5 (C); *m/z* (EI) 252 (26%, M^+), 148 (68%, M^+- NBn), 91 (93%, $C_7H_7^+$), 77 (27%, $C_6H_5^+$); (Found: C, 71.37; H, 4.80; N, 11.11. Calculated for $C_{15}H_{12}N_2O_2$: C, 71.42; H, 4.79; N, 11.10%).

(8) (a) R. Wegler, *J. Prakt. Chem.*, **1937**, *148*, 135; (b) N. P. Buu-Hoï, H. Le Bihan and F. Binon, *Recl. Trav. Chim. Pays-Bas*, **1951**, *70*, 1099.

1-Methyl-2-(3-methylbut-1-ynyl)pyridinium iodide (37); ^{1}H spectrum at 200 MHz in $CDCl_3$



2-(2-Isopropylpyrazolo[1,5-*a*]pyridin-3-yl)-1-methylpyridinium iodide (38); ^{1}H spectrum at 400 MHz in $CDCl_3$ / DMSO-d_6