An Improved Method for the Preparation of 1-Methyl-2-formyl-5-bromopyrrole†

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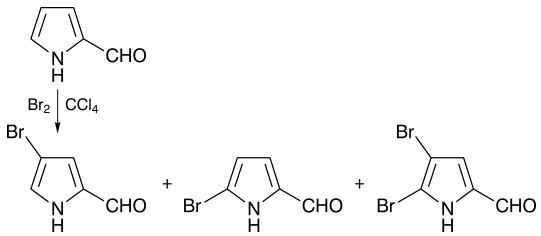
1-Methyl-2-formyl-5-bromopyrrole **1** was prepared in 48% total yield by initial bromination of the intermediate 1-methyl-2-(5,5-dimethyl-1,3-dioxan-2-yl)pyrrole **5** with *N*-bromosuccinimide to give the intermediate 1-methyl-2-(5,5-dimethyl-1,3-dioxan-2-yl)-5-bromopyrrole **6**, which was finally hydrolyzed to the product **1**.

In our first study of the correlation of UV spectra of heterocyclic aromatic compounds, *i.e.* 1-methyl-2-formyl-5-Y-substituted pyrroles,[1,2] it was necessary for us to prepare 1-methyl-2-formyl-5-bromopyrrole **1**. However, there are few reports about the bromination of pyrrolecarbaldehyde, although various types of brominating agents, *i.e.* molecular bromine, the bromonium ion, and the bromine atom, have been described.[3]

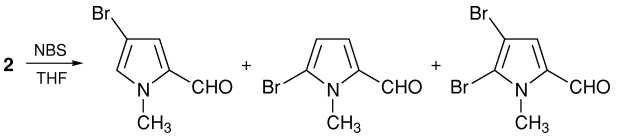
An early report[4] on the bromination of 2-formylpyrrole involved the use of bromine in carbon tetrachloride (see Scheme 1). it was found that the electron-withdrawing formyl group provided a 4-directing effect. For example, the bromination reaction at 0 °C, with equimolar 2-formylpyrrole and bromine, gave 2-formyl-4-bromopyrrole and 2-formyl-5-bromopyrrole in 60.7% and only 2.1% yield, respectively. Bromine attack is much less selective at the boiling point of carbon tetrachloride, and the amount of 5-bromo product approached that of 4-bromo product (yield: *ca.* 20%); 2-formyl-4,5-dibromopyrrole was formed simultaneously, and this made it difficult to purify each component of the product mixture by column chromatography.



Scheme 1

Another report by Meakins[5] on the bromination of 1-methyl-2-formylpyrrole **2** involved the use of bromine and $AlCl_3$. With equimolar **2** and Br_2, only 1-methyl-2-formyl-4-bromopyrrole **3** was formed.

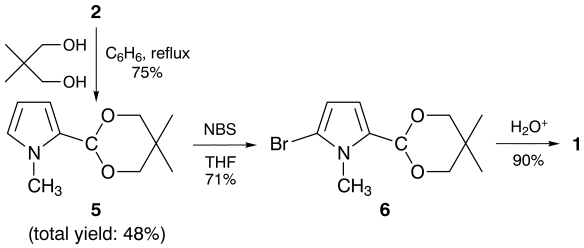
Since the above-mentioned regioselectivity of bromination was poor, we first attempted the Vilsmeier formylation of 1-methyl-2-bromopyrrole with $POCl_3$–DMF (DMF = dimethylformamide).[6] However, no detectable amount of 1-methyl-2-formyl-5-bromopyrrole **1** was formed. We then attempted the direct bromination of **2** with *N*-bromosuccinimide (NBS) (see Scheme 2). With equimolar **2** and NBS, the reaction gave one product which could be isolated pure together with a mixture of **1** and 1-methyl-2-formyl-4,5-dibromopyrrole **4** in 62 and 17% yield, respectively. The ^{1}H NMR spectrum of the above pure product was identical with that of **3**, but its melting point (50–51 °C) was different from the melting point (93–95 °C) reported by Meakins. After careful repetition of the reported reaction, the melting point of pure **3** obtained in our laboratory was again found to be 50–51 °C. Therefore, the main pure product isolated from the reaction of **2** and NBS was demonstrated as **3**. The close R_f value and boiling point of **1** (R_f = 0.94) and **4** (R_f = 0.90) made it impossible to separate them either by common column chromatography or by vacuum distillation. Although pure **1** could be isolated by reducing the relative amount of NBS, the yield (*ca.* 7%) was too low for synthetic purposes.



2 : NBS	**3** (%)	**1** (%)	**4** (%)
1 : 0.8	71[a]	7[a]	0
1 : 1	60[a]	5[b]	12[b]
1 : 1.5	18[a]	0	48[a]

Scheme 2 [a]Isolated yield of pure product; [b]yield evaluated from ^{1}H NMR spectrum

Since an electron-withdrawing group often directs the substitution to the 4-position while an electron-releasing group directs the substitution to the 5-position,[7] it would be interesting to find out what would happen if the electron-withdrawing formyl group were converted to the dioxanyl group. This idea inspired us to look for a new method for the preparation of **1** (see Scheme 3).



Scheme 3

By azeotropic distillation of **2** with 2,2-dimethylpropane-1,3-diol, 1-methyl-2-(5,5-dimethyl-1,3-dioxan-2-yl)pyrrole **5** could be obtained in 75% yield. With equimolar **5** and NBS, the reaction gave one product **6** in 71% yield. Mass spectrometry clearly showed only one molecular ion peak for the monobromo product and the ^{1}H NMR spectrum showed that the bromine atom was at the 5-position. Acid hydrolysis of **6** could easily produce the original formyl group and **1** was obtained in 90% yield. Thus, **1** could be prepared with a 48% total yield based on **2** by the improved bromination method.

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†This is a **Short Paper** as defined in the Instructions for Authors, Section 5.0 [see *J. Chem. Research (S)*, 1998, Issue 1]; there is therefore no corresponding material in *J. Chem. Research (M)*.

Experimental

1-Methylpyrrole was purchased from Tokyo Chemical Industry Co., Ltd. and redistilled before use. Solvents were purified and dried by standard procedures. Light petroleum (bp 60–90 °C) was used. Melting points were recorded on a Buchi-535 instrument and are uncorrected. The IR, ^{1}H NMR and mass spectra were recorded on a Shimadzu IR-440, a Varian FX-90Q (Me_4Si as internal standard) and an HP 5989A MS instrument respectively. All reactions were carried out under nitrogen.

Repeated Bromination of **2** *with* Br_2–$AlCl_3$.—Compound **2** was prepared by the known method, bp 63 °C at 6 Torr (lit.,[8] 76 °C at 11 Torr). Pure **3** was produced in 50% yield according to the method reported by Meakins.[5] Its melting point (50–51 °C) is different from that reported (93–95 °C).

Direct Bromination of **2** *with NBS*.—To a stirred solution (−20 °C) of **2** (9.0 g, 82 mmol) in dry tetrahydrofuran (THF) (200 ml) was added NBS (14.6 g, 82 mmol). After the NBS had dissolved, the solution was allowed to stand in a freezer for 24 h. The solvent
was evaporated *in vacuo* and the residue was separated by column chromatography (silica gel). Elution of the column with light petroleum–EtOAc (4:1) gave colorless needles of **3** (9.3 g, 60%) and a mixture of **1** and **4** (2.0 g, *ca.* 17%). The yields of **1** and **4** as evaluated by ^{1}H NMR spectroscopy were 5 and 12%, respectively. Vacuum distillation (bp 78–83 °C/at 0.4 Torr) still gave the mixture of **1** and **4**.

The foregoing experiment was repeated with a different molar ratio of **2** and NBS. When the molar ratio of **2** to NBS was 1:0.8, the reaction gave colorless needles at **1** and colourless needles of **3** in 7% and 71% yield, respectively. When the molar ratio of **2**: NBS was 1:1.5, the reaction gave colorless needles of **3** and colorless needles of **4** in 18 and 48% yield, respectively (*cf.* Scheme 2).

1, $R_f = 0.94$, mp 63–64 °C. ν/cm^{-1} (KBr) 1654 (CO), 1465, 1421, 1359, 1031, 778, 763; δ($CDCl_3$) 9.35 (s, 1 H, CHO), 6.83 (d, 1 H, 3-H, J_{3-4} 4.0 Hz), 6.27 (d, 1 H, 4-H, J_{3-4} 4.0 Hz), 3.94 (s, 3 H, NCH_3); *m*/*z* (%) 190 (7.5), 189 (100), 188 (M^+, 92.0), 187 (90.4), 186 (79.0) (Found: C, 38.36; H, 3.12; N, 7.33. C_6H_6NBrO requires C, 38.22; H, 3.22; N, 7.45%).

3, $R_f = 0.70$, mp 50–51 °C. ν/cm^{-1} (KBr) 1661 (CO), 1386, 1366, 1180, 827, 782; δ($CDCl_3$) 9.54 (s, 1 H, CHO), 6.91 (s, 2 H, 3-H and 5-H), 3.96 (s, 3 H, NCH_3); *m*/*z* (%) 190 (7.3), 189 (96.3), 188 (M^+, 100), 187 (90.3), 186 (86.8).

4, $R_f = 0.90$, mp 118–119 °C (lit.,[5] 118–120 °C). δ($CDCl_3$) 9.30 (s, 1 H, CHO), 6.89 (s, 1 H, 3-H), 3.96 (s, 3 H, NCH_3); *m*/*z* (%) 269 (43.6), 268 (61.5), 267 (M^+, 86.3), 266 (100.0), 265 (47.0), 264 (44.0).

Improved Bromination of **2** *with NBS*.—Compound **5** was prepared by the known method[9] in 75% yield.

To a stirred solution (−20 °C) of **5** (3.0 g, 15 mmol) in dry THF (100 ml) was added NBS (2.7 g, 15 mmol). After stirring for 30 min, the solution was allowed to stand in a freezer overnight. The solvent was evaporated *in vacuo* and the residue was separated by column chromatography (silica gel). Elution of the column with light petroleum–EtOAc (4:1) gave colorless needles of **6** (2.9 g, 71%). $R_f = 0.94$, mp 107–108 °C. δ($CDCl_3$) 6.17 (d, 1 H, 3-H, J_{3-4} 4.0 Hz), 6.04 (d, 1 H, 4-H, J_{3-4} 4.0 Hz), 5.31 (s, 1 H, O–CH–O), 3.69 (s, 3 H, NCH_3), 3.67 (s, 4 H, acetal CH_2), 1.27, 0.79 (s, each 3 H, acetal CH_3); *m*/*z* (%) 276 (14.0), 275 (100.0), 274 (M^+, 42.4), 273 (93.0), 272 (27.5), 194 (48.2).

To a stirred solution of **6** (2.9 g, 10 mmol) in acetone (10 ml) was added 1 M HCl (20 ml). The mixture was stirred at 50 °C for 2 h and then cooled to room temperature. The mixture was extracted with Et_2O (4 × 50 ml) and dried (Na_2SO_4). The solvents were evaporated *in vacuo* and the residue was separated by column chromatography to afford only one product **1** (1.8 g, 90%).

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