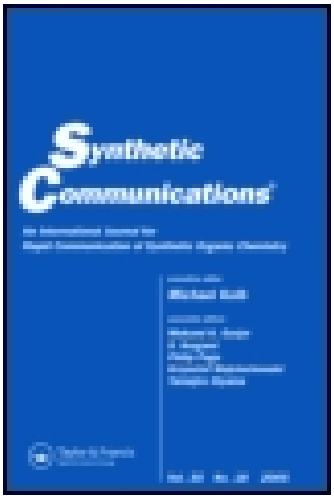

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Metallation of 2,4-Dialkoxy-5-bromopyrimidine and Formylation with Dimethylformamide: Isolation of 2,6-Dialkoxy-5-dimethylaminopyrimidine-4-carboxaldehyde

Soumita Mukherjee [a] & Binay K. Ghorai [a]
[a] Department of Chemistry , Bengal Engineering and Science University , Shibpur, Howrah, West Bengal, India
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METALLATION OF 2,4-DIALKOXY-5-BROMOPYRIMIDINE AND FORMYLATION WITH DIMETHYLFORMAMIDE: ISOLATION OF 2,6-DIALKOXY-5-DIMETHYLAMINOPYRIMIDINE-4-CARBOXALDEHYDE

Soumita Mukherjee and Binay K. Ghorai
Department of Chemistry, Bengal Engineering and Science University, Shibpur, Howrah, West Bengal, India

Direct metallation of 2,4-dialkoxy-5-bromopyrimidine with lithium diisopropylamide and consequent trapping by dimethylformamide resulted unexpectedly in the formation of 2,6-dialkoxy-5-dimethylaminopyrimidine-4-carboxaldehyde via displacement of bromine by dimethylamine moiety of dimethylformamide.

Keywords: 2,4-Dialkoxy-5-bromopyrimidine; formylation; metallation

Reactions involving halogen substituted heterocycles with strong bases are of great importance in organic synthesis. These reactions proceed via several competing mechanisms, described in several comprehensive reviews.[1,2] One of these reaction pathways is the elimination–addition (EA) mechanism, where the position ortho to the halogen atom is first deprotonated or metallated prior to elimination of halide or metal halide. The resulting aryne can then add a nucleophile, affording the product. In the case of 5-bromopyrimidine, the existence of 4-lithio-5-bromopyrimidine was established by Kress, and trapping of that lithiated product by several carbonyl compounds was also demonstrated.[3]

Here we conducted the metallation of 2,4-dialkoxy-5-bromopyrimidine by using lithium diisopropylamide (LDA) and trapped the lithiated derivative with dimethylformamide (DMF). Analogous results were obtained after formylation of the corresponding lithiated intermediates. In each case, after formylation the bromine atom was replaced by a dimethyl amino moiety. Our detailed study of this kind of reaction is confined to 2,4-dimethoxy-5-bromopyrimidine (**1a**), where, after formylation, two products were obtained. One was the expected aldehyde [2,6-dimethoxy-5-bromopyrimidine-4-carboxaldehyde (**2a**)], and the other one was an unexpected product [2,6-dimethoxy-5-dimethylaminopyrimidine-4-carboxaldehyde (**3a**)]. We examined the reaction conditions where the formation of the anomalous

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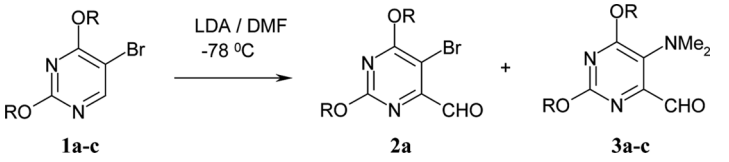
Address correspondence to Binay K. Ghorai, Department of Chemistry, Bengal Engineering and Science University, Shibpur, Howrah 711 103, West Bengal, India. E-mail: bkghorai@yahoo.co.in



1a-c 2a 3a-c

Scheme 1. Reaction of 2,4-dialkoxy-5-bromopyrimidines with LDA and DMF: **a**, R = Me; **b**, R = Et; **c**, R = nPr.

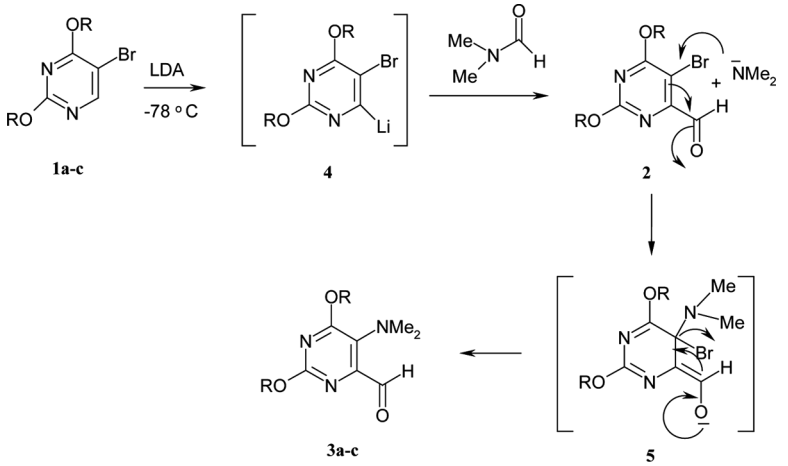
product (**3a**) can be diminished with the expected bromo aldehyde (**2a**) as the major product (Scheme 1, Table 1). Previous literature gives no report of replacement of a bromine atom by a dimethyl amine group during formylation with dimethylformamide. Numata et al.[4] had performed the metallation by lithium diisopropylamide in the case of bromopyridines, followed by electrophilic substitution of the lithiated

Table 1. Synthesis of 2,6-dialkoxy-5-dimethylaminopyrimidine-4-carboxaldehyde

			Product yield[b] (%)	
Entry	Starting materials	Conditions[a]	**2**	**3**
1	**1a**	A	**2a** (6)	**3a** (70)
2	**1a**	B	**2a** (22)	**3a** (37)
3	**1a**	C	**2a** (25)	**3a** (38)
4	**1a**	D	**2a** (52)	**3a** (28)
5	**1b**	A	—	**3b** (51)
6	**1c**	A	—	**3c** (59)

[a]Condition A: $t_1 = 10$ min, $t_2 = 1$ h, quenched at rt; condition B: $t_1 = 30$ min, $t_2 = 15$ min, quenched at −78 °C; condition C: $t_1 = 30$ min, $t_2 = 1$ h, quenched at −78 °C; condition D: $t_1 = 2$ h, $t_2 = 2$ h, quenched at −78 °C; where t_1 is time of addition of DMF after adding starting material and t_2 is time of stirring after DMF addition at −78 °C.

[b]Isolated yield.



1a-c 4 2 3a-c 5

Scheme 2. Reaction pathway to 2,6-dialkoxy-5-dimethylaminopyrimidine-4-carboxaldehyde.

derivative with DMF, but replacement of bromine by dimethyl amine moiety of DMF was not reported. This reaction behavior was found to be generalized to other alkoxy substituted pyrimidines (e.g., **1b, 1c**).

A reasonable reaction pathway for this reaction is depicted in Scheme 2. The initial step is the lithiation of the pyrimidine derivative **1** to form lithio compound **4**, which is subsequently formylated by DMF to give the expected bromo aldehyde **2**. The bromine atom adjacent to the aldehyde undergoes nucleophilic substitution by the dimethylamine anion present in the reaction medium via intermediate **5** to give dimethylamino aldehyde **3**.

These results indicate that the formation of the unexpected aldehydes **3a–c** by this mechanism increases when the reaction mixture was quenched at room temperature. The yield of desired aldehyde **2a** can be increased if quenching is done at −78°C.

EXPERIMENTAL

All melting points are uncorrected. Unless otherwise noted, all reactions were carried out under an inert atmosphere in flame-dried flasks. Solvents and reagents were dried and purified by distillation before use as follows: tetrahydrofuran (THF) from sodium benzophenone ketyl; DMF and diisopropylamine from CaH_2; and alcohols (methanol, ethanol, and n-propanol) by refluxing over magnesium turnings. After drying, organic extracts were evaporated under reduced pressure, and the residue was column chromatographed on silica gel (Spectrochem, particle size 100–200 mesh), using an ethyl acetate–petroleum ether (60–80°C) mixture as eluent.

General Procedure for Preparation of 2,4-Dialkoxy-5-bromopyrimidine[5]

Sodium metal (350 mg, 15.2 mmol) was added to dry alcohol (15 mL). When all the sodium metal was dissolved, 2,4-dichloro-5-bromopyrimidine (750 mg, 5.03 mmol) [prepared by refluxing 5-bromouracil (1.0 g), phosphorus oxychloride (14 mL), and dimethylaniline (0.5 mL) for 4 h] was added and refluxed for 2 h. The reaction mixture was cooled to room temperature, excess alcohol was removed under reduced pressure, and saturated NH_4Cl solution (5 mL) was added. The mixture was extracted with diethyl ether (3×10 mL), washed with brine (3 mL), and dried over anhydrous Na_2SO_4. Removal of the solvent gave **1a–c**.

2,4-Dimethoxy-5-bromopyrimidine (1a)[5]

Mp 62–64 °C, white prisms; IR (KBr, cm^{-1}): 1095 (C-Br); ^1H NMR (400 MHz, $CDCl_3$): δ 8.28 (s, 1H, ArH), 4.03 (s, 3H, OCH_3), 3.97 (s, 3H, OCH_3); MS: m/e (relative intensity): 219, 221 (M^+, $M^+ + 2$, 55, 55), 204, 206 (M^+-Me, $M^+ + 2$-Me, 12, 12), 188 (100), 102 (35).

2,4-Diethoxy-5-bromopyrimidine (1b)[5]

Mp 72–73 °C, white prisms; IR (KBr, cm^{-1}): 1085 (C-Br); ^1H NMR (300 MHz, $CDCl_3$): δ 8.28 (s, 1H, ArH), 4.49 (q, 2H, $J = 6.9$ Hz, OCH_2CH_3), 4.37 (q, 2H,

$J = 6.9$ Hz, OCH_2CH_3), 1.44 (t, 3H, $J = 6.9$ Hz, OCH_2CH_3), 1.41 (t, 3H, $J = 6.9$ Hz, OCH_2CH_3); MS: m/e (relative intensity): 247, 249 (M^+, $M^+ + 2$, 20, 20), 219, 221 (35, 35), 191, 193 (100, 100), 169 (15), 141 (5), 102 (10), 91 (30).

2,4-Dipropoxy-5-bromopyrimidine (1c)

Yellow oil, R_f (10% EtOAc/petroleum ether) 0.52; IR (KBr, cm^{-1}): 1092 (C-Br); ^1H NMR (300 MHz, $CDCl_3$): δ 8.27 (s, 1H, ArH), 4.37 (t, 2H, $J = 6.6$ Hz, OCH_2), 4.28 (t, 2H, $J = 6.6$ Hz, OCH_2), 1.90–1.70 (m, 4H, 2-CH_2CH_3), 1.02 (t, 3H, $J = 7.5$ Hz, $-CH_2CH_3$), 1.00 (t, 3H, $J = 7.5$ Hz, $-CH_2CH_3$); ^{13}C NMR (75 MHz, $CDCl_3$): δ 166.2, 163.7, 158.8, 97.7, 69.4, 69.1, 21.9, 21.7, 10.2, 10.1; MS: m/e (relative intensity): 275, 277 (M^+, $M^+ + 2$, 5, 5), 233, 235 (18, 18), 191, 193 (100, 96), 141 (55), 122 (30), 117 (52). Anal. calcd. for $C_{10}H_{15}BrN_2O_2$: C, 43.65; H, 5.50; N, 10.18. Found: C, 43.84; H, 5.64, N, 10.11.

General Procedure for Metallation of 2,4-Dimethoxy-5-bromopyrimidine

A solution of **1** (1.60 mmol) in THF (2 mL) was added dropwise to a LDA solution, prepared from n-butyllithium (1.6 M hexane solution, 4.0 mmol) and diisopropylamine (4.8 mmol) in THF (10 mL) at −78 °C for 1 h under an argon atmosphere, and the mixture was stirred at −78 °C for time t_1. After addition of DMF (3.2 mmol), the mixture was stirred for time t_2. The solution was then quenched with saturated aqueous NH_4Cl solution (2 mL). The mixture was extracted with diethyl ether (3×10 mL). The ether layer was washed with brine (2 mL) and dried over anhydrous Na_2SO_4. The compound was purified by column chromatography (silica gel, ethyl acetate/petroleum ether 1:9).

2,6-Dimethoxy-5-bromopyrimidine-4-carboxaldehyde (2a)

White needles, mp 106–108 °C; R_f (10% EtOAc/petroleum ether) 0.43; IR (KBr, cm^{-1}): 2860 (H−CO), 1695 (C=O), 1076 (C−Br); ^1H NMR (400 MHz, $CDCl_3$): δ 10.22 (s, 1H, CHO), 4.10 (s, 3H, OCH_3), 4.08 (s, 3H, OCH_3); ^{13}C NMR (125 MHz, $CDCl_3$): δ 186.8, 171.0, 164.6, 157.3, 110.9, 56.1, 55.5; MS: m/e (relative intensity): 247, 249 (M^+, $M^+ + 2$, 100, 97), 219, 221 (20, 20), 167, 169, (M^+-Br, $M^+ + 2$-Br, 5, 4), 141 (12), 110 (12). Anal. calcd. for $C_7H_7BrN_2O_3$: C, 34.03; H, 2.86; N, 11.34. Found: C, 33.83; H, 2.75, N, 11.51.

2,6-Dimethoxy-5-dimethylaminopyrimidine-4-carboxaldehyde (3a)

White needles; mp 117–118 °C; R_f (10% EtOAc/petroleum ether) 0.41; IR (KBr, cm^{-1}): 2906, 2813 (H−CO), 1664 (C=O); ^1H NMR (400 MHz, $CDCl_3$): δ 10.02 (s, 1H, CHO), 4.00 (s, 3H, OCH_3), 3.94 (s, 3H, OCH_3), 3.09 [s, 6H, $N(CH_3)_2$]; ^{13}C NMR (100 MHz, $CDCl_3$): 183.7, 174.5, 163.9, 163.5, 95.4, 54.1, 53.9, 40.7 (2C); MS: m/e (relative intensity): 234 (M^++ Na, 11), 212 (MH^+, 100), 182 (45), 169 (5), 130 (5). Anal. calcd. for $C_9H_{13}N_3O_3$: C, 51.18; H, 6.20; N, 19.89. Found: C, 51.31; H, 6.34, N, 19.81.

2,6-Diethoxy-5-dimethylaminopyrimidine-4-carboxaldehyde (3b)

White needles; mp 54–56 °C; R_f (15% EtOAc/petroleum ether) 0.53, IR (KBr, cm^{-1}): 2857, 2778 (H–CO), 1667 (C=O); ^{1}H NMR (500 MHz, $CDCl_3$): δ 10.06 (s, 1H, CHO), 4.48 (q, 2H, $J = 6.9$ Hz, OCH_2), 4.39 (q, 2H, $J = 6.9$ Hz, OCH_2), 3.10 [s, 6H, $N(CH_3)_2$], 1.41 (t, 3H, $J = 6.9$ Hz, $-CH_2CH_3$), 1.40 (t, 3H, $J = 6.9$ Hz, $-CH_2CH_3$); ^{13}C NMR (125 MHz, $CDCl_3$): δ 184.7, 174.8, 164.2, 164.1, 96.0, 63.5, 63.2, 41.2 (2C), 14.4, 14.3; MS: m/e (relative intensity): 240 (MH^+, 87), 225 (22), 212 (100), 184 (90), 156 (17), 102 (10). Anal. calcd. for $C_{11}H_{17}N_3O_3$: C, 55.22; H, 7.16; N, 17.56. Found: C, 55.54; H, 7.11, N, 17.51.

2,6-Dipropoxy-5-dimethylaminopyrimidine-4-carboxaldehyde (3c)

White solids; mp 38–39 °C; R_f (20% EtOAc/petroleum ether) 0.60, IR (KBr, cm^{-1}): 2875, 2778 (H–CO), 1666 (C=O); ^{1}H NMR (300 MHz, $CDCl_3$): δ 10.06 (s, 1H, CHO), 4.37 (t, 2H, $J = 6.6$ Hz, OCH_2), 4.28 (t, 2H, $J = 6.6$ Hz, OCH_2), 3.10 [s, 6H, $N(CH_3)_2$], 1.90–1.70 (m, 4H, 2-CH_2CH_3), 1.02 (t, 3H, $J = 7.5$ Hz, $-CH_2CH_3$), 1.00 (t, 3H, $J = 7.5$ Hz, $-CH_2CH_3$); ^{13}C NMR (75 MHz, $CDCl_3$): δ 184.6, 174.9, 164.3, 164.1, 96.0, 69.3, 68.9, 41.2 (2C), 22.1, 22.0, 10.5, 10.4; MS: m/e (relative intensity): 268 (MH^+, 33), 227 (7), 226 (57), 184 (100). Anal. calcd. for $C_{13}H_{21}N_3O_3$: C, 58.41; H, 7.92; N, 15.72. Found: C, 58.17; H, 7.95, N, 15.78.

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