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Taikyun Rho [a] & Yahaya F. Abuh [a]
[a] Department of Medicinal Chemistry Center for Drug Design and Development, College of Pharmacy, The University of Toledo, Toledo, Ohio, 43606-3390

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ONE-POT SYNTHESIS OF PYRIMIDINE-5-CARBOXALDEHYDE AND ETHYL PYRIMIDINE-5-CARBOXYLATE BY UTILIZING PYRIMIDIN-5-YL-LITHIUM

Taikyun Rho,* and Yahaya F. Abuh

Department of Medicinal Chemistry, Center for Drug Design and Development, College of Pharmacy, The University of Toledo, Toledo, Ohio 43606-3390

ABSTRACT: Pyrimidine-5-carboxaldehyde was prepared in a one-pot reaction from 5-bromo-pyrimidine via metal halogen exchange. Pyrimidin-5-yl-lithium reacted with formate ester and ethyl cyanoformate, forming respectively the aldehyde and carboxy ethyl ester.

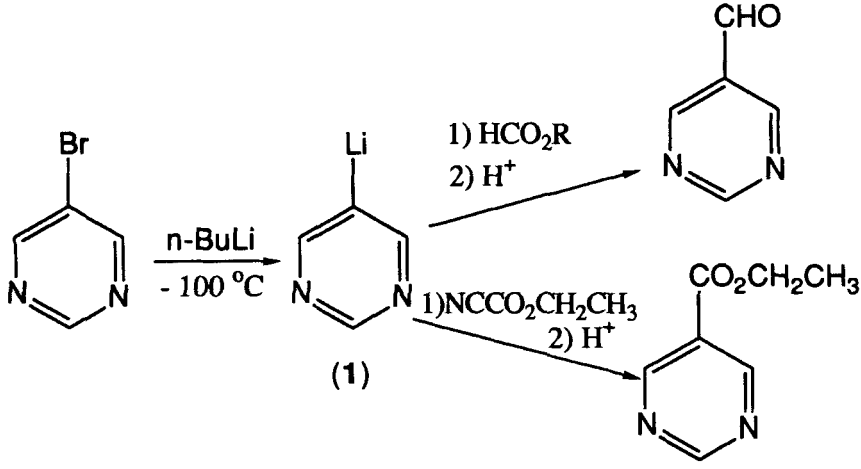
The procedure used previously for the preparation of pyrimidine-5-carboxaldehyde comprises three steps from commercially available 4,6-dihydroxypyrimidine. One of the steps includes a modified Vilsmeir reaction which requires hazardous phosgene and produces bulk of aqueous toxic waste.[1,2] The overall yield is about 25 %. During the course of study of the functionalization of pyrimidine at 5-position from 5-bromopyrimidine through metal-halogen exchange, we have achieved a one-pot synthesis of pyrimidine-5-carboxaldehyde in 59 % yield (Scheme 1).

Although the synthesis of aldehydes from the reaction of organolithium compounds and N,N-disubstituted formamide or formate ester has been well documented[3,4] and pyrimidines with alkoxy-substituents were converted to the corresponding aldehydes via the organolithium compound,[5] there has been no report of the synthesis of pyrimidine-5-carboxaldehyde from the organolithium

* To whom correspondence should be addressed.

compound. Since the pyrimidin-5-yl-lithium complex (1) is unstable above -80 °C, the reactions are carried out below -90 °C.[6] None of the reactions between (1) and orthoformate, dimethyl formamide (DMF), and N-methylformanilide (NMF) was successful to yield the aldehyde.

When (1) was reacted with formate esters (methyl formate or ethyl formate) at -100 °C and allowed to warm to 0 °C before adding water, aldehyde was obtained as a minor product. However, the anhydrous acid work-up[7] by adding etheral HCl to the mixture at -100 °C gave aldehyde in 59 % yield. This might indicate that the adduct between organolithium compound and the formate ester is not stable in this reaction medium above -80 °C.



Scheme 1

When (1) was treated with ethyl cyanoformate, the product was ethyl pyrimidine-5-carboxylate (68%). Although the addition of organolithium compound to a nitrile has been well documented,[3,4] the only major product isolated was ethyl pyrimidine-5-carboxylate, the product derived from addition of the organolithium reagent to the carbonyl, followed by elimination of the cyano group.

EXPERIMENTAL

Pyrimidine-5-carboxaldehyde

5-Bromopyrimidine (10 g, 63 mmol) and THF (600 mL; distilled over Na and benzophenone) were placed in a three-necked flask equipped with a mechanical

stirrer and a low-temperature thermometer. Dry nitrogen gas was introduced through a septum while the solution was cooled and maintained slightly above -100 °C in a liquid nitrogen-ether bath. To the vigorously stirred mixture was added 2.5 M solution of n-butyllithium in hexanes (26 mL, 65 mmol) via the septum. The yellow solution was stirred for 15 min. A solution of ethyl formate (5.0 g, 67 mmol) was added dropwise with stirring. The mixture was stirred for 20 min at -100 °C. To the cold solution was added 1.0 M ether/HCl solution (65 mL, 65 mmol, Aldrich). The etheral HCl solution was at room temperature, and was slowly added to the reaction mixture with vigorous stirring such that the internal temperature did not exceed -80 °C. Upon complete addition of the acid, the temperature of the mixture rose to -80 °C and the cold bath was removed. The mixture was stirred for an hour. The solution was concentrated to 100 mL *in vacuo*, 100 mL of water added to the yellow solution and extracted with chloroform (100 mL x 2). The organic phase was dried over $MgSO_4$, solvents removed under reduced pressure, and the residue chromatographed over silica gel column (5 x 30 cm, silica gel 60, particle size 0.04-0.063 mm, Merck) using chloroform/MeOH (9:1, v/v). Fractions containing the aldehyde (R_f = 0.4) were combined and solvents evaporated *in vacuo* to obtain an off-white semicrystalline solid (4.0 g, 59 %) . ^{1}H-nmr ($CDCl_3$): δ 10.12 (1H, s, -CHO) 9.37 (1H, s, H_2) 9.14 (2H, s, $H_{4,6}$). Calc. for $C_5H_4N_2O$: C 55.56, H 3.70, N 25.92 Found: C 55.78, H 3.84, N 25.86.

Ethyl pyrimidine-5-carboxylate

The procedure above was followed except for adding ethyl cyanoformate (6.3 g, 64 mmol) instead of ethyl formate. After work-up and flash chromatography over silica gel column (6 x 10 cm, TLC grade silica gel, Aldrich) using chloroform/hexane (8:2, v/v), the compound (R_f = 0.8 in 9:1, chloroform/ methanol) as a colorless oil (6.5 g, 68 %) was obtained. ^{1}H-nmr ($CDCl_3$): δ 9.49 (1H, s, H_2) 9.40 (2H, s, $H_{4,6}$) 4.45 (2H, q, $-CH_2-$) 1.48 (3H, t, $-CH_3$) Calc. for $C_7H_8N_2O_2$: C 55.26, H 5.26, N 18.42 Found: C 54.92, H 5.21, N 18.21.

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7. Aqueous work-up at -100 °C was not successful due to the immediate freezing of water.

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