SYNTHESIS OF 5-SUBSTITUTED PYRIMIDINES THROUGH ortho-DIRECTED LITHIATION REACTIONS

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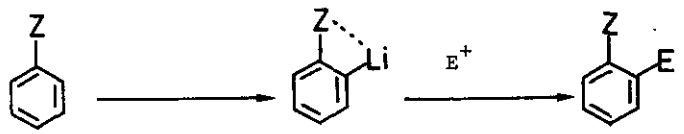
Abstract ——— Treatment of 2- and/or 4-substituted pyrimidine with LiTMP in ether at 0°C, followed by quenching with various electrophiles afforded the corresponding 5-substituted pyrimidines.

It is well known that heteroatom-facilitated lithiation of aromatics has been a powerful synthetic tool in organic chemistry due to its high regioselectivity[1] (Eq. 1). However it suffers certain limitations in heteroaromatics.[2] In pyrimidine system, the lithiation has been carried out by halogen lithium exchange[3] and there was few report[4] dealing with ortho-directed lithiation of pyrimidine having an ortho-activating group. We wish to report here the first example of the ortho-directed lithiation of 2- and/or 4-substituted pyrimidine.

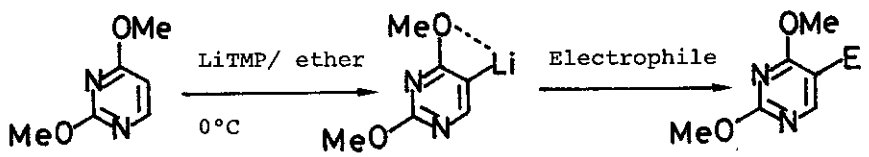


(Eq. 1)

Z= SO_2Y, CONHR, CH_2NR_2, OR
NHAr, NRAr, NR_2, etc.

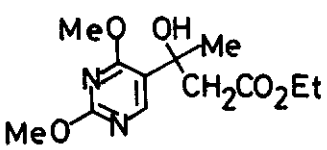
Initially, we examined ortho-directed lithiation of 2,4-dimethoxypyrimidine. Treatment of 2,4-dimethoxypyrimidine (1) in anhydrous ether with 1.2 eq of lithium diisopropylamide (LDA) at 0°C for 5 min gave 5-lithio-2,4-dimethoxypyrimidine (2), which was quenched with benzaldehyde to afford the 5-substituted product (3a) in only 5% yield with the recovery of the starting material (60%). The structure of 3a [bp. 160-165°C/ 3 mmHg; m/z 246 (M^+); ν ($CHCl_3$) 3500,

1595, 1570; δ ($CDCl_3$) 8.16 (1H, s), 7.4-7.1 (5H, m), 5.81 (1H, s), 4.59 (1H,s), 3.83 (6H, s)] was established by the identification with an authentic sample, which was prepared by the halogen lithium exchange of 5-bromo-2,4-dimethoxypyrimidine, followed by treatment with benzaldehyde. When lithium 2,2,6,6-tetramethylpiperidide (LiTMP)[5] was used as a lithiating reagent, the yield of 3a was dramatically improved (65%)(Scheme I). In a similar fashion, the reactivity of ortho-lithiated pyrimidine (2) with various electrophiles such as acetaldehyde, carbon dioxide, dimethylformamide, ethyl chloroformate, trimethylsilyl chloride, and ethyl acetate was investigated, and these results were summarized in Table I. In the case of ethyl acetate as an electrophile, 5-acetyl-2,4-dimethoxypyrimidine (3g) [mp 78-79°C; m/z 182 (M^+); ν ($CHCl_3$) 1680, 1585, 1555; δ ($CDCl_3$) 8.82 (1H,s), 4.08 (3H,s), 4.04 (3H,s), 2.58 (3H, s)] and unexpected β-hydroxyester (4) [bp 150-155°C/ 3 mmHg; m/z 270 (M^+); ν ($CHCl_3$) 3500, 1715, 1590, 1565; δ ($CDCl_3$) 8.41 (1H,s), 4.48 (1H, brs), 4.03 (2H, q, J=7), 4.01 (3H, s) , 3.95 (3H, s), 3.14 (1H, d, J=16), 2.78 (1H, d, J=16), 2.53 (3H, s), 1.12 (3H, t, J=7)] were obtained in 4% and 13% yields, respectively. Hydroxyester (4) was presumably produced via the reaction of initially formed 3g with ethyl lithioacetate, which was generated from the unreacted ethyl acetate and LiTMP.



1 2

3a E=CH(OH)Ph
3b E=CH(OH)Me
3c E=CO_2H
3d E=CHO
3e E=CO_2Et
3f E=$SiMe_3$
3g E=COMe



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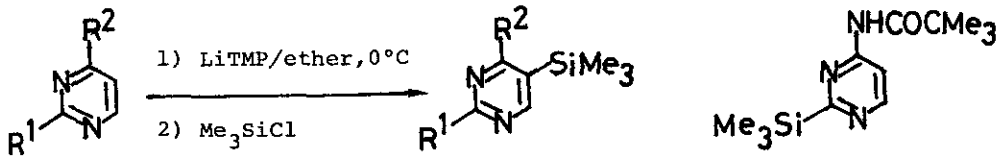
Scheme I

Table I. Reaction of 2,4-Dimethoxypyrimidine with LiTMP and Electrophiles.

Run	Electrophile	Product	Yield (%)[a]	NMR ($CDCl_3$) δ-6H
1	PhCHO	3a	65	8.16
2	MeCHO	3b	44	8.45
3	CO_2	3c	30[b]	8.73
4	Me_2NCHO	3d	24	8.78
5	$ClCO_2Et$	3e	6	8.76
6	Me_3SiCl	3f	41	8.21
7	AcOEt	3g	4	8.82
		4	13	8.41

a) Isolated yield. b) After treatment with diazomethane.

Subsequently, in order to confirm the scope and limitation of this methodology, we investigated in various pyrimidines. These pyrimidines (5a-e) were easily prepared from 2,4-dichloropyrimidine, and 5f was obtained by the reaction of 4-aminopyrimidine with pivaloyl chloride.[6] The reaction was carried out using LiTMP and trimethylsilyl chloride at 0°C (Scheme II), and these results were summarized in Table II. In the 2,4-disubstituted pyrimidines, methoxy group exhibits a stronger ortho-lithiation-directing effect than that of methoxy-ethoxy group. On the contrary, in the 4-substituted pyrimidines, the opposite result was obtained. Furthermore, when 4-pivaloylaminopyrimidine was used, the ortho-substituted product was not detectable at all and 2-substituted product (7) [m/z 251 (M^+); ν ($CHCl_3$) 1705, 1590, 1575; δ ($CDCl_3$) 8.76 (1H, d, J=5), 8.18 (1H, brs), 8.16 (1H, d, J=5), 1.39 (9H, s), 0.36 (9H, s)] was obtained in 11% yield. This result was easily understandable that the steric hindrance between the pivaloyl group with LiTMP inhibited the lithiation of 5 position, therefore the reaction was proceeded at 2 position, which was regarded to be the ortho position to the both nitrogen atoms in the pyrimidine ring.[7] Thus, we could demonstrate that the ortho-directed lithiation is possible in pyrimidine system, and further investigation is currently in progress.



5a-f 6a-e 7

Scheme II

Table II. Reaction of Various Pyrimidines with LiTMP and TMSCl.

Compound	R^1	R^2	Product	Yield (%)[a]	NMR ($CDCl_3$) δ-6H
5a	OCH_2CH_2OMe	OCH_2CH_2OMe	6a	18	8.16
5b	Cl	OCH_2CH_2OMe	6b	15	8.26
5c	Cl	OMe	6c	30	8.33
5d	H	OCH_2CH_2OMe	6d	13	8.47
5e	H	OMe	6e	5[b]	8.44
5f	H	$NHCOCMe_3$	6f	0	-

a) Isolated yield. b) Reaction temperature was -70°C.

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References and Notes

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5. M. Fieser and L. F. Fieser, "Reagents for Organic Synthesis", 1974, 4, 310.

6. Monoalkoxylation of 2,4-dichloropyrimidine and subsequent dechlorination was carried out by the reported method, see H. Yamanaka, Chem. Pharm. Bull. 1959, 7, 297 and satisfactory spectral data and/or elemental analyses were obtained for all these compounds.

7. This consideration was supported by the following facts. Using LDA as a lithiating reagent afforded 7, on the other hand, when n-BuLi was used, 2-butyl-4-pivaloylaminopyrimidine [m/z 235 (M^+); ν ($CHCl_3$) 1705, 1565, 1495; δ ($CDCl_3$) 8.61 (1H, d, J=6), 8.07 (1H, brs), 8.05 (1H, d, J=6), 2.84 (2H, t, J=7.5), 1.9-1.2 (4H, m), 0.95 (3H, t, J=7)] was obtained via the addition of n-BuLi to the C=N double bond.

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