REACTIVITY OF METHYLLITHIUM TOWARDS BRIDGEHEAD NITROGEN HETEROCYCLES

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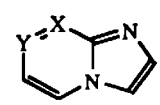
Abstract- Reactivity of methyllithium towards some bridgehead nitrogen heterocycles was investigated.

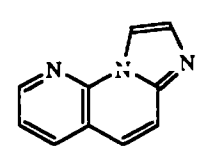
In a previous communication we have reported the reactivity of phenyllithium on some polyazaindenes (1). The results obtained prompted us to investigate other bases. Among alkyllithium derivatives, methyllithium was attractive because the reactivity of this reagent toward bridgehead nitrogen heterocycles seemed uninvestigated. Methyllithium adds to pyridine or quinoline to give 4-methyl-1,4-dihydropyridine or quinoline (2) while Peake and coworkers, obtained 2-methylquinoline by the action of methyllithium and iodine for aromatization (3). Recently Shiotani and coworkers (4), using methyllithium-lithium bromide complex at -78°C, reported the ring opening of furan cycle in 3-bromofuropyridines to give ethynylpyridinol and unsubstituted heterocycle.

In this work, we report the reaction of methyllithium on imidazo[1,2-a]pyridine (A), imidazo[1,2-a]pyrimidine (B), imidazo[1,2-a]pyrazine (C), imidazo[1,2-*c*]quinazoline (D), and imidazo[1,2-*a*][1,8]naphthyridine (E) in ether at 20°C.



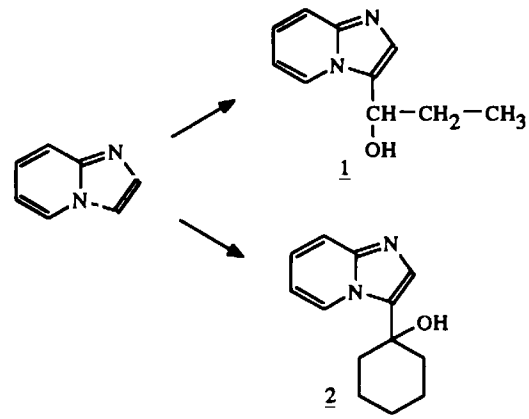
A X=CH, Y=CH
B X=N, Y=CH
C X=CH, Y=N

D



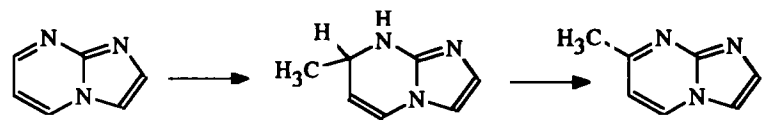
E

Imidazo[1,2-*a*]pyridine. Action of methyllithium at 20°C followed by reaction with aldehyde or ketone, gave the expected alcohol 1,2 (5) in good yield. Structures were proved by ^{1}H and ^{13}C NMR spectra.



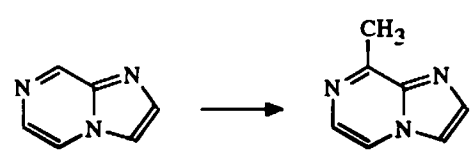
1 2

Imidazo[1,2-*a*]pyrimidine. Methyllithium at 20°C gave 7-methyl-7,8-dihydroimidazo[1,2-*a*]pyrimidine 3a in good yield. Structure was elucidated by NMR spectra, using ^{1}H-^{1}H-COSY and XH-COR. Interestingly, apparition of a second product was noted during XH-COR. After one week, transformation was complete. The derivative 3b obtained was identified as 7-methylimidazo[1,2-a]pyrimidine on the basis of NMR spectra, specially with C-7 as a quaternary carbon at 160 ppm. Formation of this compound ascertained 1,2-addition in this series.



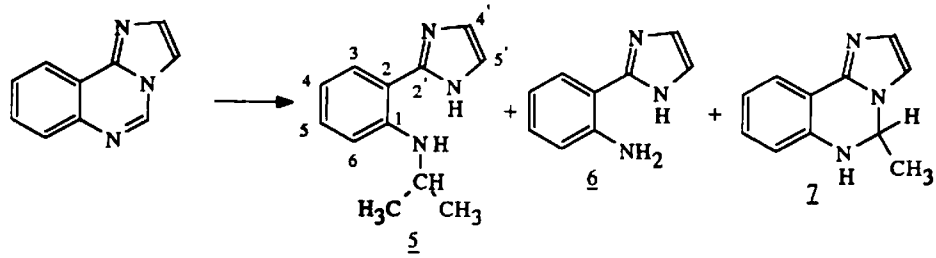
3a 3b

Imidazo[1,2-*a*]pyrazine. The 8-methylimidazo[1,2-a]pyrazine 4 was obtained in a rather low yield under the conditions described.



4

Imidazo[1,2-*c*]quinazoline. A mixture of three compounds was obtained. The first one was identified as the 2-[1'*H*-(imidazol-2'-yl)]-N-isopropylaniline 5. The second compound 6 was easily identified as the 2-[1'*H*-(imidazol-2'-yl)]aniline by comparison with a reference sample. The last compound was identified to be 5,6-dihydro-5-methylimidazo[1,2-*c*]quinazoline 7 on the basis of NMR spectra.



Imidazo[1,2-*a*][1,8]naphthyridine. Methyllithium was unreactive towards the 6,8-dimethyl derivative under the conditions described.

EXPERIMENTAL

General procedure. To a solution or suspension of the heterocyclic compound (3.8 mmol) in ether (250 ml) 1.6M methyllithium in diethylether (1.9 ml, 3.8 mmol) was added at 20°C under a flow of dry nitrogen. The resulting purple or brown solution was stirred for 1 hour. The electrophile (5 mmol) was slowly added and the resulting solution was stirred for further 1 hour. A 10% hydrochloric acid solution was added and the two layers were separated. Alcohols were extracted from the acidic medium, while other compounds were obtained from the basified aqueous layer. All the compounds were purified by column chromatography on neutral alumina with dichloromethane as eluent.

3-(1-Hydroxypropyl)imidazo[1,2-a]pyridine 1. Yield 60%; mp 146°C (Lit.(1) 143-145°C).

3-(1-Hydroxy-1-cyclohexyl)imidazo[1,2-a]pyridine 2. Yield 56%; mp 187-189°C (Lit.(5) 189-192°C); ^{13}C-NMR ($CDCl_3$, 25 MHz), δ: 21.8 (C-3',5'), 25.7 (C-4'), 36.4 (C-1',6'), 69.6 (C-1'), 111.4 (C-6), 117.6 (C-8), 123.9 (C-7), 127.2 (C-5), 129.5 (C-2), 130.38 (C-3), 146.21 (C-8a).

7-Methyl-7,8-dihydroimidazo[1,2-a]pyrimidine 3a. Yield 62%; as an oil; ^{1}H-NMR ($CDCl_3$, 400 MHz), δ: 1.26 (d, J=6.5,CH_3), 4.05 (br.s, 1H, NH), 4.37 (m, 1H, CH), 5.03 (m, 1H, H-6), 6.44 (d, J=1.7, H-5), 6.49 (m, 2H, H-2,3); ^{13}C-NMR ($CDCl_3$, 100 MHz) δ: 23.9 (CH_3), 47.6 (CH), 110.5 (C-5), 111.3 (C-6), 121.6 (C-2), 124.4 (C-3), 147.4 (C-8a); Anal. Calcd for $C_7H_9N_3$: C, 62.20; H, 6.71; N, 31.09. Found: C, 62.07; H, 6.62; N, 31.31.

7-Methylimidazo[1,2-a]pyrimidine 3b. mp 171°C (Lit. (6) 171-172°C); ^{1}H-NMR ($CDCl_3$, 400 MHz), δ: 2.59 (s, CH_3), 6.70 (d, J=7, H-6), 7.40 (d, J=1.4, H-3), 7.66 (d, H-2), 8.30 (d, J=7, H-5); ^{13}C-NMR ($CDCl_3$, 100 MHz) δ: 24.8 (CH_3), 109.6 (C-6), 110.2 (C-3), 132.8 (C-5), 134.4 (C-2), 148.5 (C-8a), 160.0 (C-7).

8-Methylimidazo[1,2-a]pyrazine 4. Yield 10%; as an oil. The ^{1}H-NMR spectra is indentical to that reported in reference (7).

2-[(1'H-(imidazol-2'-yl)]-N-isopropylaniline 5. Yield 15%; mp 107-109°C; ^{1}H-NMR ($CDCl_3$, 250 MHz), δ: 1.27 (d, J=6.3, 6H, CH_3), 3.72 (h, J=6.3, 1H, CH), 6.59 (ddd, J=8.4, 7.7 and 1.1, 1H, H-4), 6.75 (dd, J=8.3, 1.1, H-6), 7.07 (ddd, J= 8.4, 8.3 and 1.5, H-5), 7.21 (dd, J=7.8 and 1.5, H-3), 8.5 (br.s, 2H, NH); ^{13}C-NMR ($CDCl_3$, 100 MHz), δ: 22.8 (CH_3), 43.7 (CH), 111.8 (C-6), 112.0 (C-2), 114.6 (C-4), 121.6 (C-4',5'), 125.5 (C-3), 129.7 (C-5), 145.8 (C-1*), 147.0 (C-2'*); Anal. Calcd for $C_{12}H_{15}N_3$: C, 71.61; H, 7.51; N, 20.88. Found: C, 71.86; H, 7.32; N, 20.82.

2-[(1'H-(imidazol-2'-yl)]aniline 6. Yield 22%; mp 134-136°C (Lit.(8) 135-137°C).

5,6-Dihydro-5-methylimidazo[1,2-c]quinazoline 7. Yield 26%; mp 174-176°C; ^{1}H-NMR ($CDCl_3$, 250 MHz), δ: 1.71 (d, J=5.8, CH_3), 4.42 (br.s., 1H, NH), 5.48 (m, 1H, CH), 6.75 (dd, J=8 and 1, H-7), 6.90 (d, J=1.4, H-2), 6.91 (m, 1H, H-9), 7.15 (m, 1H, H-8), 7.16 (d, J=1.4, H-3), 1.90 (dd, J=7.7 and 1.5, H-10); ^{13}C-NMR ($CDCl_3$, 100 MHz), δ: 21.3 (CH_3), 63.8 (CH), 114.5 (C-2), 115.0 (C-7), 115.2 (C-10a), 120.6 (C-9), 123.7 (C-10), 129.5 (C-8), 129.7 (C-3), 140.9 (C-6a), 142.5 (C-10b); Anal. Calcd for $C_{11}H_{11}N_3$: C, 71.33, H, 5.99; N, 22.88. Found: C, 71.17; H, 6.05; N, 22.78.

^{1}H-NMR spectra were taken on Brüker AC 250 or AM 400 WB; ^{13}C-NMR spectra were obtained at 26°C with proton noise decoupling on Brüker AC 100 (25 MHz) or AM 400 WB (100 MHz) instruments. The chemical shifts are reported in ppm from TMS with the center resonance of deuteriochloroform as an internal reference for ^{13}C (77 ppm) and with the small amount of residual chloroform as an internal reference from the ^{1}H spectrum (7.24 ppm).

CONCLUSIONS

Under the conditions described, methyllithium reacts like phenyllithium but in a lower yield with imidazo[1,2-a]pyridine and pyrazine. Interestingly, addition products on the pyrimidine moiety were isolable in the imidazopyrimidine and quinazoline series. In contrast, methyllithium was ineffective towards imidazo[1,2-a][1,8]naphthyridine series.

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