REACTIVITY OF PHENYLLITHIUM TOWARD BRIDGEHEAD NITROGEN HETEROCYCLES

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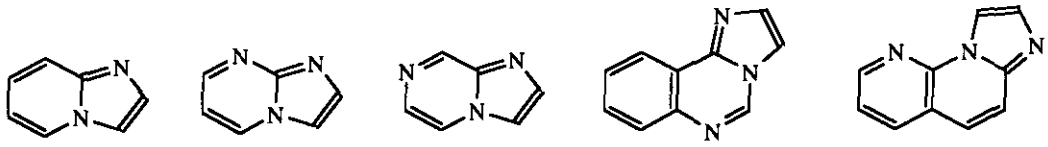
Abstract- The reactivity of phenyllithium toward some bridgehead nitrogen heterocycles was investigated. Imidazo[1,2-*a*]pyridine gave the substitution, while other series gave addition reactions. In addition, the ring opening derivative was obtained in imidazo[1,2-*c*]quinazoline series.

Reactivity of organolithium reagents on heterocycles with a bridgehead nitrogen atom, has been poorly studied. The reaction of phenyllithium on some polyazaindenes has been reported.[1] Recently, our laboratory reported that imidazo[1,2-*a*]pyridine did not react with n-BuLi, while imidazo[1,2-*a*]pyrimidine and pyrazine gave the 7 and 8-butyl derivatives respectively.[2]

The phenyllithium is a usefull reagent for metalation in benzenoid series.[3] It is well known that the reaction is satisfactory with π-deficient heterocycles derivatives while π–excessive compounds generally cause addition reactions.[3] These results were recently confirmed in polycyclic systems by Gribble *et al.*[4] who reported hydroxyalkylation at the 2-position of indole, while 2-phenyl-4-methylquinoline was obtained from 4-methylquinoline by Greenhill.[5]

In continuation of our works on the reactivity of these ring systems, we report herein the reactivity of phenyllithium on different condensed derivatives containing π-deficient and π-excessive cycles. By this way, the reaction of phenyllithium followed by propionaldehyde was studied in the imidazo[1,2-*a*]pyridine (I), pyrimidine (II), pyrazine (III), imidazo[1,2-*c*]quinazoline (IV), and imidazo[1,2-*a*][1,8]naphthyridine (V) series in ether at 0° and 20°C. The solvent effect was also studied in the case of the imidazo[1,2-*c*]-quinazoline series. More electrophilic reagents have been used in the imidazo[1,2-*a*]pyridine series.



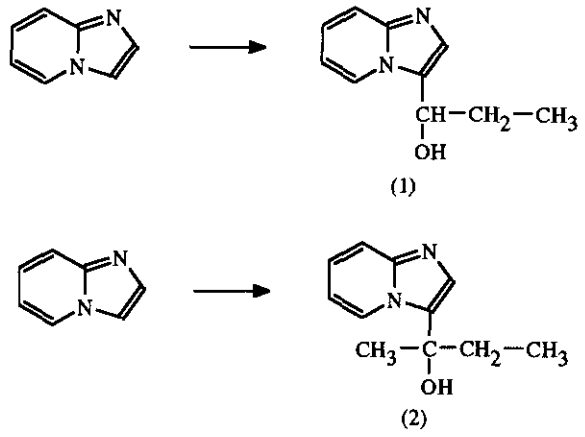
I II III IV V

Figure I

Results:

*Imidazo[1,2-a]*pyridine. The action of phenyllithium at 20°C then reaction with the aldehyde or ketone gave the expected alcohol derivatives (**1**,**2**) in good yields. Proof of the structure was done by ^{1}H-nmr with the disappearance of H-3. When the reaction was carried out at 0°C, starting material was recovered unchanged. The anion failed to react with acetonitrile, triethyl orthoformate, ethyl iodide, cyclopentene oxide, and 2-cyclohexen-1-one.

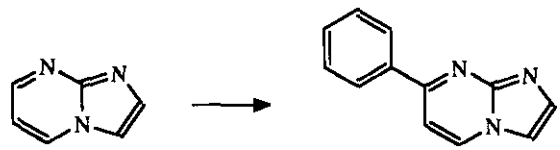
Scheme I. Reactivity of imidazo[1,2-*a*]pyridine



Reagents and Conditions. PhLi (1 eq.), ether, 20°C, 30 min, then propionaldehyde or butan-2-one, 30 min.

*Imidazo[1,2-a]*pyrimidine. The reaction with phenyllithium at 0°C and 20°C led to the 7-phenyl derivative (**3**) in high yield.

Scheme II. Reactivity of imidazo[1,2-*a*]pyrimidine

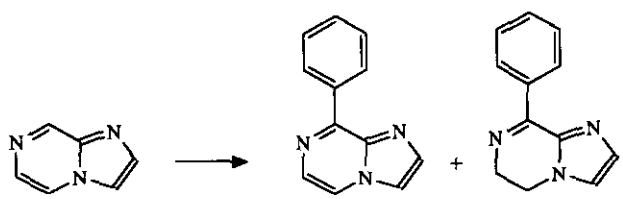


(3)

Reagents and Conditions. PhLi (1 eq.), ether, 0° or 20°C, 30 min then propionaldehyde, 30 min.

Imidazo[1,2-a]pyrazine. A set of two compounds is obtained in the reaction conditions. The first was determined to be 8-phenylimidazo[1,2-*a*]pyrazine (**4**) according to ^{1}H nmr and confirmed by mass spectral data.[6] The major compound (**5**) was determined to be the 5,6-dihydro derivative on the basis of ^{1}H nmr with a multiplet at δ 4.07 which integrated for 4H. The structure was further confirmed by ^{13}C nmr with two signals at δ 42.0 and 47.4.

Scheme III. Reactivity of imidazo[1,2-*a*]pyrazine

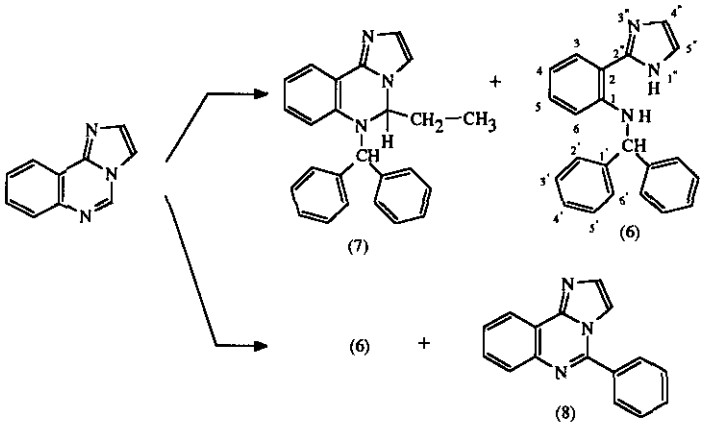


(4) (5)

Reagents and Conditions. PhLi , ether, 0° or 20°C, 30 min then propionaldehyde, 30 min.

Imidazo[1,2-*c*]quinazoline. The reaction in ether gave a mixture of two compounds (**6**,**7**). The first was determined to be 2-[1"*H*-(imidazol-2"-yl)]-1-diphenylmethylaminobenzene (**6**) on the basis of mass spectra. The structural determination was ascertained by ^{1}H and ^{13}C nmr. The complete attributions were made with the aid of ^{1}H-^{1}H COSY, HMBC, and HMQC experiments. Ring opening in an acidic media[7e] in this series was reported by us. The second derivative (**7**), which showed a triplet at δ 0.75 (3H), a doublet at 1.67 (2H), and a multiplet at 5.06 (1H), was derived from **6** by the reaction with propionaldehyde. Ring closure of (**6**) analogues has been reported by Bowie.[8] The molecular ion at *m/z*: 365 is in good agreement with the purposed structure. In THF, the reaction led to compound (**6**) along with 4-phenylimidazo[1,2-*c*]quinazoline (**8**).

Scheme IV. Reactivity of imidazo[1,2-*c*]quinazoline



Reagents and Conditions. (i) PhLi (1 eq.), ether, 0° or 20°C, 30 min then propionaldehyde, 30 min; (ii) PhLi (1 eq.), THF, 20°C, 30 min then propionaldehyde, 30 min;

Imidazo[1,2-*a*][1,8]naphthyridine. In the reaction conditions, starting material was recovered unchanged.

Conclusion: The reactivity of phenyllithium toward nitrogen bridgehead heterocycles led to various results. Phenyllithium gave the anion at the 3-position on the imidazolic ring of azine derivatives, while addition occured on the π–deficient moiety on diazines derivatives. With imidazo[1,2-*c*]quinazoline series, solvent effect was observed: In THF, phenyllithium adds to the 4-position while the major product was a ring opening derivative. In ether, ring opening and ring opening-ring closure compounds may be isolated. Phenyllithium was showed to be unreactive toward imidazo[1,2-*a*][1,8]naphthyridine. Further studies are in progress with other heterocycles, solvents, and bases.

EXPERIMENTAL.

General. Mps were determined on a Kofler hot stage and are uncorrected. ^{1}H-Nmr were recorded on Brüker AC 100, AC 250, EM 360. ^{13}C-Nmr were performed on a Brüker AC 100 (25 MHz) or EM 360 (90 MHz). Mass spectrometry was realized on a LKB 2091 spectrometer.

Phenyllithium (2 M cyclohexane/ether) was purchased from Aldrich. Starting material[7] were purified prior to used. Ether and tetrahydrofuran were dried according to a classical procedure. Electrophiles were distilled before the reactions. All experiments were made under a nitrogen atmosphere. Elemental analyses were performed by Microanalytical Center, ENSCM, Montpellier.

General procedure. To a solution or suspension of the heterocyclic compound (3.8 mmol) in ether (250 ml) or THF (250 ml) was added phenyllithium (1.9 ml, 3.8 mmol) at 0°C or 20°C under a flow of dry nitrogen. The resulting brown solution was stirred for 30 min. The electrophile (5 mmol) was slowly added and the resulting solution was stirred for further 30 min. A 10% hydrochloric acid solution was added and the two layers were separated. The alcohols were extracted from the acidic medium, while other compounds were obtained from the basified aqueous layer. All the compounds were purified by chromatography on neutral alumina eluted with dichloromethane.

3-(1-Hydroxypropyl)imidazo[1,2-a]pyridine (1). Yield 60%; mp 143-145°C; ^{1}H-nmr ($CDCl_3$, 250 MHz) δ 1.06 (t, J = 7.4 Hz, 3 H, CH_3), 2.04 (m, 2 H, CH_2), 3.00 (brs, 1 H, OH), 4.87 (t, J = 7 Hz, 1 H, CH), 6.79 (ddd, J = 6.6, 6.5, and 1.5 Hz, 1 H, H-6), 7.16 (ddd, J = 9.1, 6.5, and 1.5 Hz, 1 H, H-7), 7.23 (s, 1 H, H-2), 7.50 (dd, J = 9.1, and 1.5 Hz, 1 H, H-8), 8.35 (dd, J = 6.6, and 1.5 Hz, 1 H, H-5); ^{13}C-nmr ($CDCl_3$, 25 MHz) δ 10.7 (CH_3), 28.1 (CH_2), 67.1 (CH), 112.4 (C-6), 117.5 (C-8), 124.9 (C-7 or 5), 125.4 (C-5 or 7), 126.4 (C-3), 130.0 (C-2), 146.0 (C-8a); ms *m/z* (%) 176 (M^+, 26), 147 (M^+-Et,100), 119 (26), 78 (67). Anal. Calcd for $C_{10}H_{12}N_2O$: C, 68.18; H, 6.82; N, 15.91. Found: C, 67.91; H, 6.68; N, 16.15.

3-(1-(1-Hydroxy-1-methyl)propyl)imidazo[1,2-a]pyridine (2). Yield 56% as an oil; ^{1}H-nmr ($CDCl_3$, 100 MHz) δ 0.83 (t, J = 7.3 Hz, 3 H, CH_3), 1.62 (s, 3 H, CH_3), 1.99 (q, J = 7.3 Hz, 2 H, CH_2), 4.30 (brs, 1 H, OH), 6.70 (ddd, J = 6.6, 6.5, and 1.5 Hz, 1 H, H-6), 7.00 (s, 1 H, H-2), 7.14 (ddd, J = 9, 6.5, and 1.5 Hz, 1 H, H-7), 7.30 (dd, J = 9, and 1.5 Hz, 1 H, H-8), 8.72 (dd, J = 6.6, and 1.5 Hz, 1 H, H-5); ^{13}C-nmr ($CDCl_3$, 25 MHz) δ 8.7 (CH_3), 28.3 (CH_3), 33.0 (CH_2), 71.2 (C-1'), 111.5 (C-6), 117.3 (C-8), 123.9 (C-7), 127.7 (C-5), 129.0 (C-3), 129.7 (C-2), 146.0 (C-8a). Anal. Calcd for $C_{11}H_{14}N_2O$: C, 58.41; H, 6.19; N, 12.39. Found: C, 58.21; H, 6.32; N, 12.18.

7-Phenylimidazo[1,2-a]pyrimidine (3). Yield 80%; mp 172-174°C (lit.[9] mp 172°C); ^{13}C-nmr ($CDCl_3$, 25 MHz) δ: 106.1 (C-6), 110.5 (C-3), 127.3 (C-3',5'), 128.8 (C-2',5'), 130.5 (C-4'), 133.3 (C-2), 135.7 (C-5), 136.9 (C-1'), 148.9 (C-8a), 156.6 (C-7); ms *m/z* (%) 195 (M^+, 100), 194 (34), 140 (10), 92 (41).

8-Phenylimidazo[1,2-a]pyrazine (4). Yield 14% as an oil; ^{1}H-nmr ($CDCl_3$, 250 MHz) δ 7.55 (m, 3 H, H_{phenyl}), 7.74 (d, J = 1.4 Hz, 1 H, H-2 or 3), 7.87 (d, J = 1.4 Hz, 1 H, H-3 or 2), 7.99 (d, J = 4.5 Hz, 1

H, H-5 or 6), 8.07 (d, J = 7.2 Hz, 1 H, H-5 or 6), 8.64 (m, 2 H, H_{phenyl}); ms *m/z* (%) 195 ($M^{+\cdot}$,100), 194 (57), 169 (35), 142 (10). Anal. Calcd for $C_{12}H_9N_3$: C, 73.85; H, 4.61; N, 21.54. Found: C, 73.97; H, 4.82; N, 21.21.

8-Phenyl-5,6-dihydroimidazo[1,2-a]pyrazine (**5**). Yield 50%. mp 111-113°C; ^{1}H-nmr ($CDCl_3$, 250 MHz) δ 4.07 (m, 4 H, $2CH_2$), 6.97 (d, J = 0.9 Hz, 1 H, H-2 or 3), 7.20 (d, J = 0.9 Hz, 1 H, H-3 or 2), (m, 3 H, H_{phenyl}), 8.12 (m, 2 H, H_{phenyl}); ^{13}C-nmr ($CDCl_3$, 25 MHz) δ 42.0 (CH_2), 47.4 (CH_2), 120.1 (C-3), 128.1 (C-2',6' or C-3',5'), 128.9 (C-3',5' or C-2',6'), 129.5 (C-4' or 2), 130.3 (C-2 or 4'), 135.9 (C-8*), 138.3 (C-1*), 158.2 (C-8a); ms *m/z* (%) 197 ($M^{+\cdot}$, 100), 196 (57), 169 (65). Anal. Calcd for $C_{12}H_{11}N_3$: C, 73.10; H, 5.58; N, 21.32. Found: C, 72.92; H, 5.62; N, 21.46.

2-[(1"*H*-(imidazol-2"-yl)]-1-diphenylmethylaminobenzene (**6**). Yield 65%. mp 185-187°C; ^{1}H-nmr ($CDCl_3$, 360 MHz) δ 5.67 (s, 1 H, CH), 6.63 (ps.t, J = 7.4, and 1.1 Hz, 1 H, H-4), 6.66 (d, J = 8.5 Hz, 1 H, H-6), 7.04 (s, 2 H, H-4",5"), 7.11 (ps.t, J = 8.5, and 7.4 Hz, 1 H, H-5), 7.27 (m, 2 H, H-4'), 7.35 (m, 4 H, H-3',5'), 7.46 (dd, J = 7.5, and 1.5 Hz, 1 H, H-3), 7.49 (m, 4H, H-2',6'), 9.35 (brs, 2 H, 2NH); ^{13}C-nmr ($CDCl_3$, 90 MHz) δ 62.4 (CH), 112.4 (C-2), 112.7 (C-6), 115.6 (C-4), 121.6 (C-4",5"), 125.5 (C-3), 127.0 (C-4'), 127.3 (C-2',6'), 128.6 (C-3',5'), 129.7 (C-5), 143.1 (C-1'), 145.5 (C-1), 146.4 (C-2"); ms *m/z* (%) 325 ($M^{+\cdot}$, 62), 248 (26), 182 (29), 160 (95), 77 (11). Anal. Calcd for $C_{22}H_{19}N_3$: C, 81.23; H, 5.85; N, 12.92. Found: C, 81.01; H, 5.97; N, 13.02.

5,6-dihydro-5-ethyl-6-diphenylmethylimidazo[1,2-c]quinazoline (**7**). Yield 12% as an oil; ^{1}H-nmr ($CDCl_3$, 250 MHz) δ 0.75 (t, J = 7.4 Hz, 3 H, CH_3), 1.67 (m, 2 H, CH_2), 5.06 (m, 1 H, H-5), 5.49 (s, 1 H, CH), 6.59 (d, J = 1.1 Hz, 1 H, H-3), 6.82 (m, 1 H, H-7), 7.07 (m, 2 H, H_{phenyl}), 7.09 (d, J = 1.1 Hz, 1 H, H-2), 7.20 (m, 10 H, H_{phenyl}), 7.94 (m, 1 H, H-10); ms *m/z* (%) 365 ($M^{+\cdot}$, 8), 336 (20), 197 (20), 167 (100), 152 (25). Anal. Calcd for $C_{25}H_{23}N_3$: C, 82.19; H, 6.30; N, 11.51. Found: C, 82.29; H, 6.39; N, 11.32.

4-Phenylimidazo[1,2-c]quinazoline (**8**). Yield 10%. mp 127-129°C; ^{1}H-nmr ($CDCl_3$, 250 MHz) δ 7.60 (m, 4 H, H-2, $3H_{phenyl}$), 7.66 (m, 1 H, H–8), 7.71 (m, 1 H, H–9), 7.73 (d, J = 1.5 Hz, 1 H, H-2), 7.96 (m, 2 H, H_{phenyl}), 8.01 (m, 1 H, H–7), 8.58 (m, 1 H, H-10); ^{13}C-nmr ($CDCl_3$, 25 MHz) δ 113.2, 122.7, 128.4, 128.5, 128.6 (2CH), 129.2 (2CH), 130.2, 131.2, 132.5; ms *m/z* (%) 245 ($M^{+\cdot}$, 100), 123 (11), 77 (13). Anal.

Calcd for $C_{16}H_{11}N_3$: C, 78.37; H, 4.49; N, 17.14. Found: C, 78.12; H, 4.54; N, 17.34.

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