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The addition of organolithium reagents to the azomethine bond of 5,6-disubstituted pyrimidines provided, in every case, a single adduct. When reacted with either ethyl chloroformate or hydrogen chloride, these adducts gave a single dihydro pyrimidine. The resulting N-H dihydro pyrimidines were oxidized with potassium permanganate to the corresponding pyrimidines.

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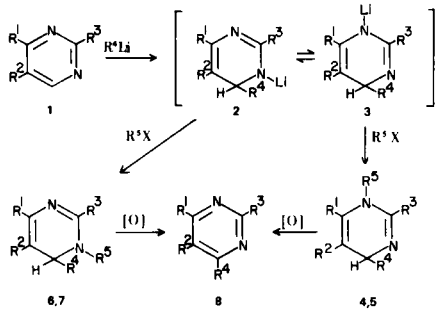
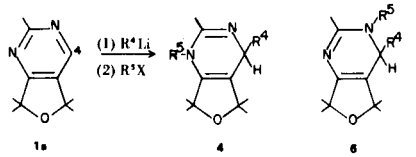
The 1,2-addition of organolithium compounds to the azomethine bond of pyridines was first reported in 1930 by Ziegler (1), and the 1,4-addition (2) and 1,2-diaddition (3) to pyridines have since been reported. More recently, Giam (4) has examined the alkylation and acylation of these organolithio pyridine adducts.

It was our intent to explore the reactivity of 5,6-disubstituted pyrimidines toward organolithium reagents, and of the resulting organolithio pyrimidine adducts with acyl halides or mineral acids. As our model systems we



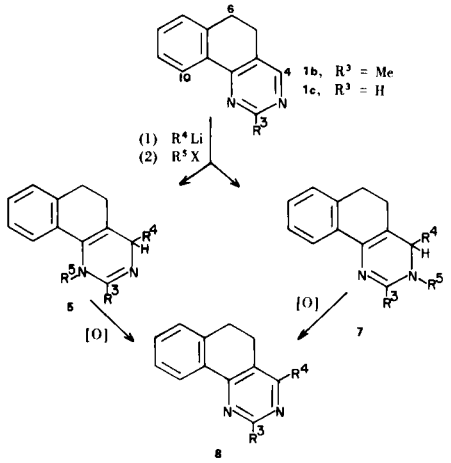
chose the bicyclic furo[3,4-*d*]pyrimidine (**1a**), and the tricyclic benzo[*h*]quinazolines (**1b** and **1c**).

The organolithium reagents included aliphatic (*n*BuLi) aromatic (PhLi), heterocyclic (2-picolyl Li) and dilithio (*N*,2-dilithio *N*-methyltoluamide) (5) species. With **1a**, there is a single unsubstituted site on the pyrimidine ring, C-4, yet there are two factors working against organolithium addition. First, the *gem*-di-Me substitution at C-5 might sterically hinder attack at C-4. Also, the C-2-Me protons are sufficiently acidic (6) so as to undergo exchange with and thereby quench the organolithium reagent. Despite these potential problems, the reaction proceeded with each of the four organolithium reagents in high yields at 0°, with organolithium addition only at C-4. Quenching of the organolithium pyrimidine adduct (**2** and/or **3**) could provide either of two dihydro pyrimidines, **4** or **6**, yet only a single product was



observed in all cases. The assignment of structure 4 to this product, albeit tentative, was based on its proton nmr versus that of the starting material **1a**. Each of the Me signal has moved significantly upfield and, as one might expect for either **4** or **6**, all four of the aliphatic Me's have become non-equivalent. In the case of **4d**, a hydrochloride salt, the upfield shift of the Me groups is offset by the effects of protonation. With the phenyl lithium adducts **4b** and **4c** one of the Me signals is shifted upfield by over 0.4 ppm. On examination of Dreiding models one notices that with these compounds, one of the Me groups lies above the plain of the aromatic ring, thus explaining its pmr absorption.

With **1b** there is again only one unsubstituted site on the pyrimidine ring, C-4. Sterically, the N-1 site, as evidenced by the downfield shift of the aromatic C-10 H, is most hindered, an effect which will manifest itself more during the second or quenching step of the reaction sequence. There are now acidic protons at C-5 and C-6 as well as on the C-2 methyl group. Once again despite



these factors, organolithium addition of all four reagents at 0° followed by quenching with either ethyl chloroformate or hydrogen chloride gas proceeded in high yield, to give only one of the two possible dihydro compounds **5** or **7**. With isomer **5**, saturation at N-1 would lead to an easing of the C-10 H, N-R^5 steric interaction resulting in an upfield shift of C-10 H absorption in the proton nmr.

Table 1

Compound	R^3	R^4	R^5	M.p. °C (B.p. °C/mm Hg)	Yield %	Empirical Formula (M.W.)	Elemental Analysis Calcd./Found C	H	N	Cl	Procedure
4a	Me	*n*-Bu	CO_2Et	54-55	76	$C_{18}H_{30}N_2O_3$ (322.44)	67.1 67.4	9.4 9.4	8.7 8.5		A
4b	Me	Ph	CO_2Et	(100-100/0.2)	64	$C_{20}H_{26}N_2O_3$ (342.42)	70.2 70.6	7.7 8.0	8.2 7.8		A
4c	Me	Ph	H	185-186	89	$C_{17}H_{20}N_2O$ (270.41)	75.5 75.3	8.2 8.2	10.4 10.1		C
4d	Me	*o*-$CH_2C_6H_4CONHMe$	H	185-190	82	$C_{20}H_{27}N_3O_2 \cdot 1\ 1/2HCl$ (396.19)	60.6 60.4	7.3 7.5	10.6 10.2	13.4 12.9	B
4e	Me	2-Picolyl	CO_2Et	(120-130/0.1)	72	$C_{20}H_{27}N_3O_3$ (357.44)	67.2 67.4	7.6 7.2	11.8 11.6		A
5a	Me	Ph	CO_2Et	(170-180/0.1)	72	$C_{22}H_{22}N_2O_2$ (346.41)	76.3 76.8	6.4 6.6	8.1 7.7		A
5b	H	Ph	H	182-188	75	$C_{18}H_{16}N_2 \cdot HCl$ (296.82)	72.8 72.3	5.8 5.9	9.4 9.2	11.9 12.0	B
5c	Me	Ph	H	131-136	96	$C_{19}H_{18}N_2 \cdot HCl$ (310.85)	73.4 73.8	6.2 6.1	9.0 8.6	11.4 11.4	B
5d	H	2-Picolyl	H	189-191	67	$C_{18}H_{17}N_3 \cdot 2HCl$ (348.30)	62.1 62.6	5.5 5.6	12.1 11.9	20.4 19.9	B
5e	H	2-Picolyl	CO_2Et	(150-160/0.5)	86	$C_{21}H_{21}N_3O_2$ (347.40)	72.6 72.7	6.1 6.2	12.1 12.4		A
5f	H	*o*-$CH_2C_6H_4CONHMe$	H	118 dec.	68	$C_{21}H_{21}N_3O$ (331.45)	76.1 76.4	6.4 5.2	12.7 12.3		B
8a	H	Ph	--	109-110	82	$C_{18}H_{14}N_2$ (258.34)	83.7 83.5	5.5 5.6	10.8 10.3		D
8b	Me	Ph	--	180-182	86	$C_{19}H_{16}N_2 \cdot 3/4HCl$ (308.82)	75.5 75.5	5.6 5.4	9.3 9.1	8.6 8.4	D
8c	H	2-Picolyl	--	120-122	28	$C_{18}H_{15}N_3 \cdot 2HCl$ (346.28)	62.4 62.2	5.0 5.0	12.1 12.0	20.5 20.7	D
8d	H	*o*-$CH_2C_6H_4CONHMe$	--	154-157	46	$C_{21}H_{19}N_3O$ (329.39)	76.6 76.2	5.8 5.8	12.8 12.8		D

Table 2

Partial Spectral Data

Compound	Nmr (a)	Ir (b)
4a	0.89 (broad t, 3H), 1.10-1.40 (m, 21H), 2.47 (s, 3H), 4.29 (q, J = 6 Hz, 2H), 4.79 (broad t, J = 4 Hz, 1H)	1715, 1685
4b	0.87 (s, 3H), 1.20-1.60 (m, 12H) with [1.33 (s, 3H), 1.38 (s, 3H), 1.54 (s, 3H)], 2.23 (s, 3H), 4.26 (q, J = 7 Hz, 2H), 5.65 (s, 1H), 7.25 (s, 5H)	1710, 1680
4c	0.65 (s, 3H), 1.30 (s, 3H), 1.36 (s, 3H), 1.40 (s, 3H), 1.99 (s, 3H), 5.24 (s, 1H), 7.33 (s, 5H)	3450, 1670
4d	1.42 (s, 3H), 1.48 (s, 3H), 1.52 (s, 3H), 1.56 (s, 3H), 2.15 (s, 3H), 2.78 (ABq, J = 5,14 Hz, 1H), 2.98 (d, J = 5 Hz, 3H) 3.37 (ABq, J = 5,14 Hz, 1H), 4.75 (t, J = 5 Hz, 1H), 7.28 (s, 5H), 7.44 (d, J = 5 Hz, 1H)	3450, 3300, 1655
4e	1.00-1.50 (m, 15H), 2.41 (s, 3H), 2.90 (d of ABq, 2H), 4.05 (q, J = 7 Hz, 2H), 5.15 (t, J = 5 Hz, 1H), 6.95-7.70 (m, 3H), 8.51 (m, 1H)	1715, 1680
5a	1.35 (t, J = 7 Hz, 3H), 2.20-3.00 (m, 7H) with [2.49 (s, 3H)], 4.30 (q, J = 7 Hz, 2H), 5.60 (s, 1H), 7.10-7.50 (m, 8H), 7.85 (m, 1H)	1695
5b	1.80-2.95 (m, 4H), 5.34 (s, 1H), 7.00-7.50 (m, 8H), 7.90 (m, 1H), 8.40 (broad s, 1H)	1685, 1640
5c	1.80-2.90 (m, 7H), 5.24 (s, 1H), 7.08-7.40 (m, 9H), 8.20 (broad s, 1H)	1675, 1640
5d	2.00-3.20 (m, 6H), 4.74 (t, J = 5 Hz, 1H), 6.90-7.70 (m, 7H), 8.40-8.95 (m, 2H)	1685, 1635
5e	1.28 (t, J = 7 Hz, 3H), 2.23 (m, 2H), 2.65-3.15 (m, 4H), 4.20 (q, J = 7 Hz, 2H), 5.06 (t, J = 5 Hz, 1H), 7.00-7.85 (m, 7H), 7.96 (s, 1H), 8.54 (m, 1H)	1720, 1635
5f	2.20-3.50 (m, 9H) with [2.96 (d, J = 4 Hz, 3H)], 6.90-7.70 (m, 9H)	3450, 3260, 1650, 1600
8a	2.70-3.20 (m, 4H), 7.20-7.70 (m, 8H) 8.41 (m, 1H), 9.22 (s, 1H)	1610
8b	3.06 (broad s, 4H), 3.19 (s, 3H), 7.20-7.80 (m, 8H), 8.58 (m, 1H)	1605
8c	2.70-4.05 (m, 6H), 7.20-9.55 (m, 9H)	1630, 1610
8d	2.96 (d, J = 5 Hz, 3H), 3.07 (s, 4H), 4.32 (s, 2H), 6.95-7.60 (m, 7H), 8.34 (m, 2H), 8.98 (s, 1H)	3470, 3260, 1600

(a) Recorded on a Varian T-60 or XL-100 Spectrometer, expressed in δ relative to TMS. (b) Recorded on a Perkin-Elmer model 257 or 457 spectrometer expressed in cm^{-1}.

Such is the case, with the shift being more dramatic in the cases where $R^5 = CO_2Et$ than where $R_5 = H \cdot HCl$.

In the case of **1c** there are now two unsubstituted sites on the pyrimidine ring. Because electronic repulsion between the N lone pair and the organolithium reagent would be greater at C-2 than at C-4 one would expect addition to occur primarily at C-4. In each example, organolithium addition at 0° followed by quenching with either ethyl chloroformate or hydrogen chloride gas provided a single dihydro product. Proof as to the position of organolithium attack was provided by the facile oxidation with potassium permanganate of these dihydro products. The proton nmr's of the resulting oxidation products **6** clearly displayed a C-2 H absorption. Thus initial organolithium attack must have occurred at C-4 and not at C-2. One can again, based on the proton nmr spectra assign structure **5** and not **7** to the dihydro products. It must be emphasized that the assignment of structure **5** to the compounds prepared by organolithium addition followed by ethyl chloroformate or hydrogen chloride quench is tentative, and is based solely on chemical shifts observed in the proton nmr spectra of these compounds. What is significant, no matter whether these intermediates are of structural type **4,5** or **6,7** is that is all cases only a single product results, and that it is formed in high yield.

With the exception of starting materials no products other than those reported could be isolated. In none of the reactions was any attempt made to maximize yields. The pertinent data is summarized in Table 1.

EXPERIMENTAL

The ir spectra were recorded on a Perkin Elmer Model 257 or 457 grating spectrophotometer and nmr spectra were recorded using either a Varian T-60 or EM-360 spectrometer. ^{13}C nmr spectra were recorded using a Varian XLFT-100 spectrometer. Chemical shifts (δ) are recorded relative to TMS, coupling constants (J) are given in Hertz. Mass spectra were recorded using either an LKB 9000 or an AEI MS-30-D5-50 spectrometer. Melting points were obtained on a Thomas-Hoover capillary melting point apparatus and are uncorrected. In all workup procedures, the drying process involved swirling over magnesium sulfate and filtering prior to evaporation. The partial spectral data is summarized in Table 2. The starting materials **1a**, **1b** and **1c** were prepared by literature procedures (8).

Procedure A.

Organolithium Addition Followed by Ethyl Chloroformate Quench.

To a solution of pyrimidine **1a** (1.92 g., 10 mmoles) in ether (30 ml.) at 0° under nitrogen was added dropwise a 1.6 *N* hexane solution of *n*-BuLi (6.25 ml., 20 mmoles). After an additional 0.5 hours at 0°, a solution of ethyl chloroformate (1 ml., 10.5 mmoles) in ether (5 ml.) was added rapidly, during which time the red precipitate which had formed during *n*-BuLi addition was replaced by a white precipitate. Filtration through Celite and evaporation of the filtrate gave a yellow oil which on distillation (110-120°/0.2) yielded 2.45 g. (76%) of dihydropyrimidine **4a** as a clear oil which crystallized on standing, m.p. 54-55°.

Following this procedure compounds **4b**, **4e**, **5a** and **5e** were similarly prepared. Literature procedures were used to prepare the dilithiotoluamide (5) and picolyl lithium (7).

Procedure B.

Organolithium Addition Followed by Hydrogen Chloride Quench.

After addition of the organolithium reagent to pryimidine **1a** at 0° under nitrogen in a manner similar to that described in Procedure A and an additional 0.5 hours at 0°, a stream of hydrogen chloride gas was passed through the cooled solution until saturation had occurred. After evaporation of the solvent, *in vacuo*, the residue was extracted several times with chloroform and the combined chloroform extracts evaporated. The resulting residue, after being washed with ether to remove any traces of starting material was crystallized from dichloromethane-ether affording a 67% yield of **4d** as a white solid, m.p. 185-190°.

Using this procedure, compounds **5b**, **5c**, **5d** and **5f** were similarly prepared.

Procedure C.

Hydrolysis of Carbamate **4b**.

A mixture of carbamate **4b** (0.342 g., 1 mmole) and potassium hydroxide (0.24 g. of 80%, 5 mmoles) in methyl cellosolve (2 ml.) was stirred at ambient temperature for 4 hours. Ether (50 ml.) was added and the mixture was filtered through Celite, dried and evaporated to give a yellow oil. Crystallization from ether-hexane gave 240 mg. (89%) of a white solid, m.p. 185-186°.

Procedure D.

Oxidation of Dihydropyrimidine **5f**.

To a solution of dihydropyrimidine **5f** (0.331 g., 1 mmole) in acetone (5 ml.) was added dropwise a 0.125 *M* aqueous solution of potassium permanganate (8.7 ml., 1.1 mmoles). The resulting mixture was allowed to stir at ambient temperature for 2 hours, then poured into water (25 ml.) and extracted thoroughly with ether. The combined ether extracts were dried and evaporated, and the residue recrystallized from isopropyl ether to give 0.150 g. (46%) of pyrimidine **8d** as white crystals, m.p. 154-157°.

With this procedure, compounds **8a**, **8b** and **8c** were similarly prepared.

Acknowledgements.

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