

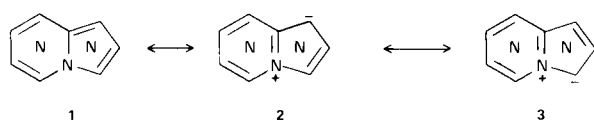
Phenyllithium Addition Reactions of Some Polyazaindenes

William W. Paudler, C. I. Patsy Chao and Larry S. Helmick

Department of Chemistry, Clipping Laboratories, Ohio University, Athens, Ohio 45701

Received May 11, 1972

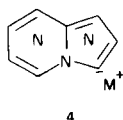
The Chemistry of Polyazaindenes (**1**) has received considerable attention during the past ten years (1,2,3,4,5).



These studies have demonstrated that the compounds are aromatic and that they are subject to electrophilic substitution in the five-membered ring. The reactivity of some of the sigma C-H bonds is exemplified by the results of H-D exchange studies under basic catalysis. These exchanges are facilitated by *N*-alkylation of the non-bridge nitrogen atoms in the five-membered rings and demonstrate, among other things, that resonance contributors of type **2** and **3** play a significant part in their contribution to the ground-state structure of these compounds.

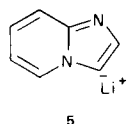
A consideration of these resonance contributors suggests that the six-membered rings of these polyazaindenes should be reactive toward alkyl and aryl lithium compounds and similar substances.

These addition reactions would, however, be expected to compete with the known reactivity of some of the compounds toward the formation of salts of type **4**.

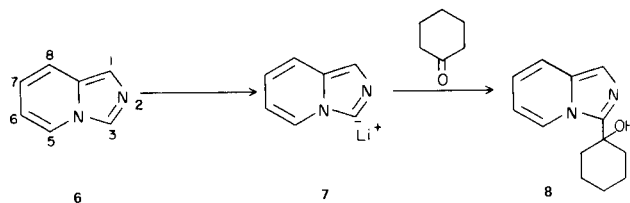


Thus, the competition between these two reactions would control their outcome.

We have already described the reaction of phenyllithium with imidazo[1,2-*a*]pyridine and have shown that the anion **5** is formed in this reaction (1).



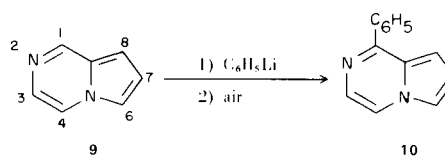
A similar reaction on imidazo[1,5-*a*]pyridine (**6**) has now afforded the anion **7**, as established by the formation of its "trapping" product **8**.



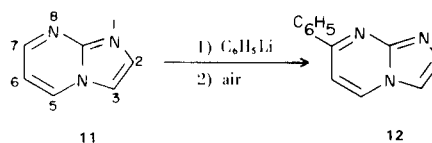
The structure proof of this compound rests upon its elemental analysis, mass spectrometric molecular weight and an analysis of its pmr spectrum in comparison to that of the starting material (see Table I).

When these reactions are attempted on any of the polyazaindenes with an additional ring-nitrogen atom in the six-membered ring, the resulting compounds are phenylated derivatives of these polyazaindenes. Thus, the addition reactions in these cases proceed more rapidly than the generation of the ether insoluble lithium salts of the potential polyazaindene anions.

The reaction of phenyllithium with pyrrolo[1,2-*a*]pyrazine (**9**) affords a monophenyl derivative whose pmr spectrum is devoid of the H-1 singlet. The remainder of the pmr spectrum is consistent with the assigned structure, 1-phenylpyrrolo[1,2-*a*]pyrazine (**10**) (see Table I).



The treatment of imidazo[1,2-*a*]pyrimidine (**11**) with phenyllithium affords a monophenyl derivative whose pmr spectrum shows the presence of two AB systems. The chemical shifts of these protons, in comparison with those of the parent compound (see Table I) are consistent with the assigned structure, 7-phenylimidazo[1,2-*a*]pyrimidine (**12**).



When *s*-triazolo[1,5-*a*]pyrimidine (**13**) is treated with phenyllithium, two monophenyl derivatives are obtained. A comparison with authentic samples (**6**) identifies these compounds as the 5-phenyl (**14**) and the 7-phenyl (**15**) *s*-triazolo[1,5-*a*]pyrimidines, respectively.

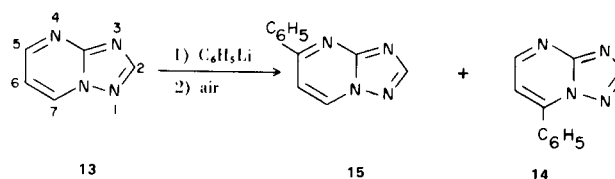


TABLE Ia

Proton Chemical Shifts of Some Polyazaindenes (a)

Compd. No.	Ring Proton Position								Substituent
	H ₁	H ₂	H ₃	H ₄	H ₅	H ₆	H ₇	H ₈	
6	2.62	-----	1.95	-----	2.17	3.48	3.48	2.65	nil
8	2.72	-----	-----	-----	1.46	3.58	3.37	2.72	>CH 7.04, >CH ₂ 7.8-8.5
9	1.09	-----	2.42	2.11	-----	2.54	3.03	3.15	nil
10	-----	-----	2.37	2.22	-----	2.50	3.06	3.08	2.0-2.5 (multiplets)
11	-----	2.23	2.39	-----	1.28	3.09	1.40	-----	nil
12	-----	2.15	2.39	-----	1.51	2.51	-----	-----	2.1-2.5 (multiplets)
18	-----	1.48	1.52	-----	-----	1.95	1.97	-----	nil
19	-----	1.12	-----	-----	-----	2.00	2.04	-----	2.0-2.6 (multiplets)

(a) Values are in units of τ , as dilute solutions in deuteriochloroform.

TABLE Ib

Proton-Proton Coupling Constants of Some Polyazaindenes (b)

Compd. No.	J ₁₄	J ₁₅	J ₁₆	J ₂₃	J ₃₄	J ₃₈	J ₄₈	J ₅₆	J ₅₇	J ₅₈	J ₆₇	J ₆₈	J ₇₈
6		0.5				1.0		7.2	0.9	1.1	6.4	1.1	9.2
8		0.5						7.4	1.0	1.2	6.4	1.1	9.1
9	1.55		1.0		5.5		0.8				2.5	1.5	4.5
10					5.5		0.8				2.4	1.5	4.0
11				1.4				6.9	2.0		4.1		
12				1.4				6.9					
18				1.8							1.6		
19											1.7		

(b) Values are in Hz.

TABLE II

Experimental Data for Phenyllithium Reactions

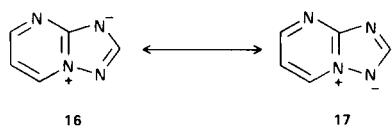
Starting Material	A (mmoles)	B (mmoles)	C (hours) (a)	Yields (a)	Products No.
Pyrrolo[1,2- <i>a</i>]pyrazine (9)	5.1	11.5	12	29.6	10
Imidazo[1,2- <i>a</i>]pyrimidine (11)	3.7	7.4	12	48.0	12
Imidazo[1,2- <i>b</i>]as-triazine (18)	2.9	6.0	12	10.5	19
<i>s</i> -triazolo[1,5- <i>e</i>]pyrimidine (13)	8.5	17.0	12	9 6	14 15

(a) The various reactions were also carried out with shorter reaction times. The highest yields were obtained when the reactions were allowed to proceed for 12 hours.

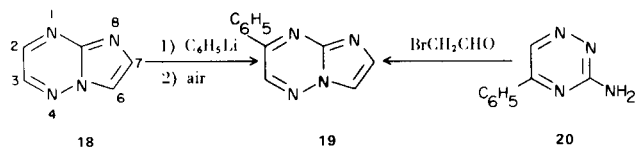
TABLE III
Analytical Data for Various Phenyl Substituted Azaindolizines

Compounds	m.p.	Formula	C	Elemental Analyses				
				Calcd. H	N	C	Found H	N
10	156.5°	C ₁₉ H ₁₃ N ₅ O ₇ (picrate)	53.90	3.07	16.55	53.63	3.38	16.39
19	173°	C ₁₂ H ₉ N ₃	73.85	4.62	21.54	73.73	4.66	21.71
12	153°	C ₁₁ H ₈ N ₄	67.35	4.08	28.57	67.51	4.35	28.71

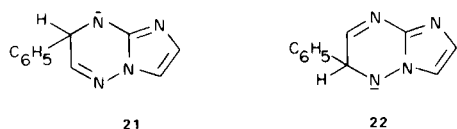
Thus, we find the first example of the addition of phenyllithium in a position adjacent to the bridge nitrogen atom in these polyazaindolizines. This may well be caused by the greater electron delocalization into the five-membered ring due to the contribution of resonance structures **16** and **17** to the ground-state structure of this molecule.



Finally, the reaction of imidazo[1,2-*b*]-*as*-triazine (**18**) with phenyllithium affords, again, a monophenyl derivative whose structure was established as the 2-phenyl derivative **19** by its unequivocal synthesis from 3-amino-5-phenyl-*as*-triazine (**20**) (5).

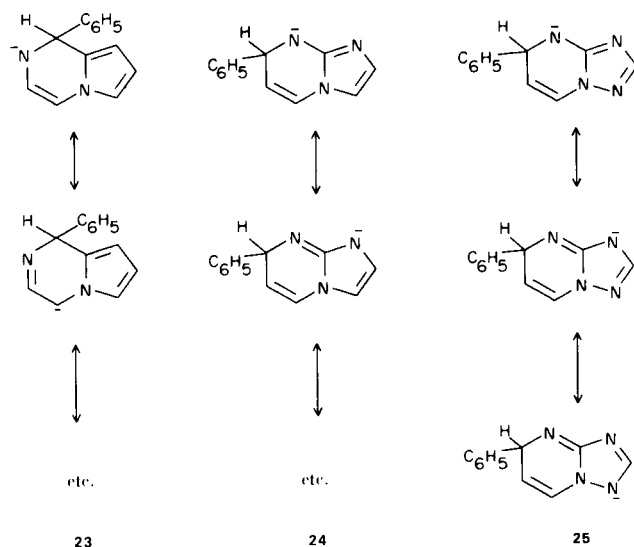


The lack of formation of any 3-phenyl-imidazo[1,2-*b*]-*as*-triazine can possibly be rationalized by considering the two intermediates **21** and **22** in the phenylation reaction since only structure **21** can be resonance stabilized



by involvement of N-8, while structure **22** cannot.

The intermediates involved in the phenylation of pyrrolo[1,2-*a*]pyrazine (**9**), imidazo[1,2-*a*]pyrimidine (**11**), and of *s*-triazolo[1,5-*a*]pyrimidine (**13**) can be similarly stabilized by involvement of structures **23**, **24** and **25**, respectively.



EXPERIMENTAL (7)

General Procedure for the Phenyllithium Reactions.

To a stirred solution of the appropriate polyazaindolizine (*A* mmole), Table II in 20 ml. of dry dioxane (nitrogen atmosphere) was added, dropwise, *B* mmole of a 2.30 M solution of phenyllithium in a 70:30 mixture of benzene-ether. The reaction mixture was stirred for *C* hours and the reaction was stopped by the addition of absolute methanol (20 ml.). The mixture was then cautiously acidified with 2 *N* hydrochloric acid and extracted with chloroform. The aqueous solution was made basic with sodium carbonate and exhaustively extracted with chloroform. This chloroform extract was then dried over sodium carbonate, filtered, and evaporated to dryness to yield the crude product. Column chromatography on neutral alumina (Grade III) and elution with benzene and ethyl acetate mixtures gave the corresponding products. Vacuum sublimation of these substances afforded pure products as determined by nmr, tlc, elemental analyses, molecular weight determinations from mass spectral data and melting points. The yields and analytical data for the various compounds are listed in Table II and III.

3-(1-Hydroxycyclohexyl)imidazo[1,5-*a*]pyridine (**8**).

To a stirred solution of 354 mg. (3 mmoles) of imidazo[1,5-*a*]pyridine (**6**) in 20 ml. of dried dioxane was added, dropwise, a

solution of 504 mg. (6 mmoles) of phenyllithium in 10 ml. of benzene. The mixture was stirred at room temperature for 10 minutes and 600 mg. (6 mmoles) of cyclohexanone was added, and the resulting mixture was stirred for 10 hours. The reaction was stopped by the addition of water (20 ml.) and the organic layer was separated and extracted with 5% aqueous hydrochloric acid. The combined acidic solutions were washed with chloroform and the aqueous layer was made basic with sodium carbonate and extracted with chloroform. These combined extracts were then dried over anhydrous sodium carbonate and filtered. The filtrate was concentrated under reduced pressure and the residue was chromatographed on neutral alumina (Grade III). Elution with benzene and ethyl acetate mixtures yielded 78 mg. (10% of theory) of compound **8**, m.p. 215-217°, (see Table I for pmr data).

Anal. Calcd. for $C_{13}H_{16}N_2O$: C, 72.25; H, 7.41; N, 12.96. Found: C, 72.05; H, 7.56; N, 13.07.

REFERENCES

Since the number of references is legion, only some key references are given.

- (1) W. W. Paudler and H. G. Shin, *J. Org. Chem.*, **33**, 1638 (1968).
- (2) B. Loez and M. M. Goodman, *Tetrahedron Letters*, 789 (1968).
- (3) L. Petit and P. Touratier, *Bull. Soc. Chim. France*, 2529 (1966).
- (4) P. J. Black, M. L. Hefferman, L. M. Jackman, Q. N. Porter and G. R. Underwood, *Aust. J. Chem.*, **17**, 1128 (1964).
- (5) T. K. Chen, "1,2,4-Triazine," Ph.D. thesis, Ohio University, Athens, Ohio, 1971.
- (6) K. Shirakawa, *Yakugaku Zasshi*, **80**, 956 (1960).
- (7) The molecular weights of all compounds were obtained with a Hitachi-Perkin Elmer instrument. The pmr spectra were recorded with a Varian HA-100 Spectrometer. Elemental analyses were performed by the Analytical Services division of the Ohio University Chemistry Department.