Lithium Amide Catalyzed Amine–Olefin Addition Reactions

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This paper describes the addition of amines to vinyl aromatics and 1,3 dienes catalyzed by lithium amides. The lithium amide is generated *in situ* by adding the desired amount of butyllithium to the reaction mixture containing amine and vinyl aromatic or 1,3 diene. This technique provides a convenient route to alkylalkenyl- and alkylarylamines. High yields are obtained under mild reaction condition.

Reactions of amines with vinylic compounds have been known for some time. The most familiar examples include the host of condensations of acrylates and vinyl ketones with ammonia and amines which result in amino-substituted esters, amides, nitriles, and the like.[1]

The reactions of dienes and vinyl aromatics with amines has not been so widely studied. Aniline, in the presence of 20 g-atom % metallic sodium, is reported[2,3] to condense with butadiene and with isoprene at 120°, giving 79% yields of *N*-crotylanilines in 18 hr. Acid catalysis of aniline–butadiene condensations results[4] in a mixture of ring and N-substitution products at 230–260°.

More closely related to our system is the work of Martirosyan,[5] who claimed the preparation of a series of amines by passing butadiene through ether solutions of alkylamines in the presence of catalytic quantities of sodium metal at 25°. The adducts, obtained in 60–92% yields, appeared to be 1,4 adducts. Wegler and Pieper found that alkylamines add to styrene in the presence of 1–3 wt % sodium metal, give β-phenethylamines in 8–80% yields when refluxed for 3–5 hr.[6]

In our work, we discovered that the reactions of lithium alkylamides, generated *in situ* from alkylamines and butyllithium, in catalytic quantities promote amine–olefin addition reactions, providing a convenient synthetic route to tertiary amines. *n*-Butyllithium and *sec*-butyllithium were used interchangeably.

Results

Addition to Vinyl Aromatic Compounds.—Cyclic and acyclic primary and secondary amines add to vinyl aromatics with the aid of butyllithium in catalytic quantities. The products, substituted β-phenethylamines, are summarized in Table I.

Secondary amines, such as di-*n*-nonylamine and diethylamine, add with ease to styrene, no. 1–5. A slight increase in the rate of reaction is implied when tetrahydrofuran is used in place of cyclohexane as the solvent. The same yield is obtained in tetrahydrofuran with a shorter reaction time, 23 hr compared to 4 hr. Monocyclic and dicyclic amines, piperidine, and 1,3-di(4-azacyclohexyl)propane add to styrene to give high yields, no. 6–8, with shorter reaction times than the aliphatic amines of no. 1–5. This suggests a steric influence on the addition reaction. Primary amines react with 2 equiv of styrene, and no product of monoaddition was detected even with one equivalent of styrene, no. 9–11. Ammonia, however, does not react with styrene under these conditions.

Vinyl aromatics other than styrene may be successfully used in this reaction, as evidenced by the reaction of piperidine with α-methylstyrene, 1,1-diphenylethylene, and *trans*-stilbene, no. 13–16.

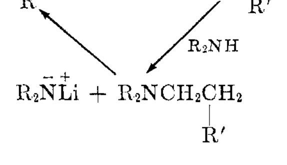
Addition to Dienes.—Dienes, such as butadiene and isoprene, react with amines, in the presence of a catalytic amount of butyllithium. The product mixture depends on the solvent employed and the structure of the amine (Table II). In cyclohexane, piperidine adds predominantly 1,4 to 1,3-butadiene, giving 63% trans and 36% cis adduct, no. 1, while 2,6-dimethylpiperidine gives an 80:20 trans–cis product ratio, no. 3, and diethylamine a 20:79 trans–cis product ratio, no. 4. In all three cases, the 1,2-piperidine adduct with 1,3-butadiene is ≤1% of the total product. The isomers were separated by gas chromatography and identified by either uv or nmr spectroscopy.

A change to the polar solvent tetrahydrofuran produces dramatic shifts in adduct stereochemistry. Both piperidine and diethylamine add 1,4 to 1,3-butadiene to give 99% trans adduct, no. 2 and 5. Only traces of other isomers are present. This shift may well be due more to solubility than any other factor. Lithium diethylamide and lithium piperidine, thought to be the initially formed species, are slightly soluble in hydrocarbons; the high cis adduct may thus be a result of a heterogeneous system. Tetrahydrofuran solubilizes both of these lithium salts permitting a homogeneous reaction system. A detailed study of the reaction mechanism(s) was not attempted.

Piperidine and diethylamine add predominantly 4,1 to isoprene, no. 6 and 7. The product with piperidine contains 76% 4,1 adduct accompanied by small amounts of other isomers. Diethylamine gives only the 4,1 adduct.

Discussion

The catalyzed reaction of amines with olefins apparently involves the initial addition of a lithium amide to the olefin, followed by proton transfer from amine to



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[5] G. T. Martirosyan, E. A. Grigoryan, and A. T. Babayan, *Izv. Akad. Nauk. Arm. SSR, Khim. Nauki*, **17**, 517 (1964).

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TABLE I

AMINE ADDITIONS TO VINYL AROMATICS[a]

No.	Amine	Vinyl aromatic	Time, hr	Yield, %	Product	Registry no.
1	$(C_2H_5)_2NH$	$C_6H_5CH{=}CH_2$	23	57	$(C_2H_5)_2NCH_2CH_2C_6H_5$[f,g]	5300-21-0
2	$(C_2H_5)_2NH$	$C_6H_5CH{=}CH_2$	4[b]	58	$(C_2H_5)_2NCH_2CH_2C_6H_5$[f]	
3	$(n\text{-}C_3H_7)_2NH$	$C_6H_5CH{=}CH_2$	16	47	$(n\text{-}C_3H_7)_2NCH_2CH_2C_6H_5$[f-h]	23916-02-1
4	$(n\text{-}C_9H_{19})_2NH$	$C_6H_5CH{=}CH_2$	16	41	$(n\text{-}C_9H_{19})_2NCH_2CH_2C_6H_5$[f,i]	31165-60-3
5	$(CH_3)(n\text{-}C_4H_9)NH$	$C_6H_5CH{=}CH_2$	16	70	$(CH_3)(n\text{-}C_4H_9)NCH_2CH_2C_6H_5$[f,j]	36794-44-2
6	$C_5H_{11}N$ (piperidine)	$C_6H_5CH{=}CH_2$	5	81	$C_5H_{10}NCH_2CH_2C_6H_5$[f,n]	332-14-9
7	$C_5H_{11}N$	$C_6H_5CH{=}CH_2$	5[b]	88	$C_5H_{10}NCH_2CH_2C_6H_5$[f]	
8	$(4\text{-}C_5H_{10}NCH_2)_2CH_2$	$C_6H_5CH{=}CH_2$[c]	8	80	$[C_6H_5CH_2CH(NC_5H_{10}\text{-}4)CH_2]_2CH_2$[f,k]	36794-46-4
9	$n\text{-}C_3H_7NH_2$	$C_6H_5CH{=}CH_2$[c]	16	33	$n\text{-}C_3H_7N(CH_2CH_2C_6H_5)_2$[f,g]	27974-01-2
10	$n\text{-}C_4H_9NH_2$	$C_6H_5CH{=}CH_2$[c]	16	47	$n\text{-}C_4H_9N(CH_2CH_2C_6H_5)_2$[f,l]	24068-19-7
11	$n\text{-}C_5H_{11}NH_2$	$C_6H_5CH{=}CH_2$[c]	16	32	$n\text{-}C_5H_{11}N(CH_2CH_2C_6H_5)_2$[f,m]	36794-49-7
12	NH_3	$C_6H_5CH{=}CH_2$	16[d]	0		
13	$C_5H_{11}N$	$(C_6H_5)(CH_3)C{=}CH_2$	5[b,e]	71	$(C_6H_5)(CH_3)CHCH_2C_5H_{10}N$[f,g]	36794-50-0
14	$C_5H_{11}N$	$(C_6H_5)(CH_3)C{=}CH_2$	6	42	$(C_6H_5)(CH_3)CHCH_2C_5H_{10}N$[f]	
15	$C_5H_{11}N$	$(C_6H_5)_2C{=}CH_2$	48[e]	82	$(C_6H_5)_2CHCH_2C_5H_{10}N$[f,g,o]	36794-51-1
16	$C_5H_{11}N$	*trans*-$C_6H_5CH{=}CHC_6H_5$	48	10	$C_6H_5CH_2CH(C_6H_5)(C_5H_{10}N)$[f,g]	36794-52-2

[a] 13% (w/w) reactants in cyclohexane; 50°; 5 mol % butyllithium, based on the amine; 1 mol of styrene/mol of amine. [b] Solvent, tetrahydrofuran. [c] 2 mol of styrene/mol of amine. [d] Room temperature. [e] 2 mol of amine/mol of vinyl aromatic. [f] Identification by ir. [g] Identification by picrate formation and comparison with known sample. [h] *Anal.* Calcd for $C_{14}H_{23}N$: C, 81.95; H, 11.22; N, 6.83. Found: C, 81.80; H, 11.20; N, 7.19. [i] *Anal.* Calcd for $C_{26}H_{47}N$: C, 83.65; H, 12.60; N, 3.75. Found: C, 81.90; H, 13.38; N, 4.75. [j] *Anal.* Calcd for $C_{13}H_{21}N$: C, 81.68; H, 10.99; N, 7.33. Found: C, 81.69; H, 11.10; N, 7.22. [k] *Anal.* Calcd for $C_{29}H_{40}N_2$: C, 83.25; H, 10.05; N, 6.70. Found: C, 83.20; H, 10.16; N, 6.71. [l] *Anal.* Calcd for $C_{20}H_{27}N$: C, 85.40; H, 9.60; N, 4.98. Found: C, 84.11; H, 10.23; N, 5.81. [m] *Anal.* Calcd for $C_{21}H_{29}N$: C, 85.42; H, 9.83; N, 4.75. Found: C, 84.45; H, 10.59; N, 6.16. [n] *Anal.* Calcd for $C_{13}H_{19}N$: C, 82.54; H, 10.05; N, 7.41. Found: C, 81.88; H, 10.07; N, 8.58. [o] *Anal.* Calcd for $C_{19}H_{23}N$: C, 86.04; H, 8.68; N, 5.28. Found: C, 85.57; H, 8.85; N, 5.71.

TABLE II

AMINE ADDITIONS TO 1,3 DIENES[a]

No.	Amine	Solvent	Time, hr	Yield, %	Product[b]	Registry no.
					Additions to 1,3-Butadiene	
1	$C_5H_{11}N$ (piperidine)	CHX[c]	24	83	*cis*-$C_5H_{10}NCH_2CH{=}CHCH_3$ (36%)	36807-51-9
					trans-$C_5H_{10}NCH_2CH{=}CHCH_3$ (63%)	36807-52-0
					$C_5H_{10}NCH_2CH_2CH{=}CH_2$ (1%)	4088-34-0
2	$C_5H_{11}N$	THF[d]	28	58	*trans*-$C_5H_{10}NCH_2CH{=}CHCH_3$	
3	$2,6\text{-}(CH_3)_2C_5H_9N$	CHX	17	50	*trans*-$2,6\text{-}(CH_3)_2C_5H_8NCH_2CH{=}CHCH_3$ (80%)	36812-99-4
					cis-$2,6\text{-}(CH_3)_2C_5H_8NCH_2CH{=}CHCH_3$ (20%)	36813-00-0
4	$(C_2H_5)_2NH$	CHX	24	81	*cis*-$(C_2H_5)_2NCH_2CH{=}CHCH_3$ (79%)	34069-08-4
					trans-$(C_2H_5)_2NCH_2CH{=}CHCH_3$ (20%)	34069-09-5
					$(C_2H_5)_2NCH_2CH_2CH{=}CH_2$ (1%)	15431-05-7
5	$(C_2H_5)_2NH$	THF	24	48	*trans*-$(C_2H_5)_2NCH_2CH{=}CHCH_3$	
					Additions to Isoprene	
6	$C_5H_{11}N$	CHX	24	95	$C_5H_{10}NCH_2CH{=}C(CH_3)_2$ (76%)	36794-55-5
					$(C_5H_{10}NCH_2)(CH_3)C{=}CHCH_3$ (15%)	36794-56-6
					$(C_5H_{10}NCH_2CH_2)(CH_3)C{=}CH_2$ (7%)	36794-57-7
					$(C_5H_{10}NCH_2)(CH_3)CHCH{=}CH_2$ (2%)	36794-58-8
7	$(C_2H_5)_2NH$	CHX	24	57	$(C_2H_5)_2NCH_2CH{=}C(CH_3)_2$[e]	10229-36-4

[a] 13% (w/w) reactants in cyclohexane; 50°; 5 mol % *sec*-butyllithium, based on the amine; 2 mol of amine/mol of 1,3 diene. [b] Gpc separation of isomers; identification by nmr and ir. [c] CHX = cyclohexane. [d] THF = tetrahydrofuran. [e] Identification by picrate formation and comparison with a known sample.

the organolithium intermediate,[7] thereby regenerating amide anions. Schematically, the system is pictured as a competition between olefin and amine for organolithium.

The initial reaction between amide and olefin can only occur if the amide is sufficiently nucleophilic to add to the olefin. Thus, dialkylamides react, while aniline derivatives do not. The olefin itself must be activated to nucleophilic attack, and the greater the activation, the more rapid and complete the reaction. For example, vinyl aromatics add amide quite readily, while dienes react more slowly, and simple aliphatic olefins do not react with amides at all under these conditions.

For the reaction to proceed cleanly to adduct formation, the reaction between the intermediate adduct and the amine must occur very much more rapidly than the potentially competing polymerization reaction. For the 1,3 dienes and vinyl aromatics studied this is apparently the case, since no polymeric material is isolated.

The reaction of secondary amines with a large excess of 1,3-butadiene in cyclohexane in the presence of a catalytic amount of butyllithium produces the monoamine–butadiene adduct coupled with polybutadiene containing one secondary amine residue. The nature of

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[7] In amine–styrene reactions the formation of 2-lithiophenethylamines is indicated by the ultraviolet spectrum of the reaction mixture which shows a strong absorption at the wavelength expected for a benzylic anion (330 mμ).

the termination step of this polymerization is unknown. The microstructure is that expected for normal anionic polymerization, 44% cis 1,4, 48% trans 1,4, and 8% 1,2. Curiously, when an excess of styrene is employed, no polymeric material is isolated.

In summary, vinyl aromatic compounds and 1,3 dienes add amines readily in the presence of small amounts of lithium alkylamides, providing a particularly convenient route to alkylalkenyl- and alkylarylamines.

The yields are higher using milder reaction conditions than the amine–olefin reactions discussed by Wegler and Pieper.[6] For example, they prepared a β-phenethylamine in only 25% yield by reacting di-*n*-butylamine and styrene with 1–2% sodium at 150–200° for 6–8 hr. Compare to our more facile reaction in Table I. Di-*n*-propylamine reacted with styrene with a 47% yield. Martirosyan's[5] yields are also lower in reactions of amines and 1,3 dienes catalyzed by sodium. Diethylamine reacted with 1,3-butadiene at 25° with *ca.* 1% sodium at 25° with a 65% yield (compare to our data in Tables I and II). Diethylamine reacted with 1,3-butadiene catalyzed by butyllithium with an 81% yield (Table II, no. 4).

Experimental Section

sec-Butyllithium was purchased from the Foote Chemical Co. The reactants and solvents were purchased from either the Eastman Kodak Co. or the Aldrich Chemical Co. and were distilled prior to use. The reaction products reported in this paper were characterized by infrared, elemental analysis, nuclear magnetic resonance, and gas chromatography. When possible, comparison of boiling points and picrate melting points with those in the literature were made.

The following five experiments show the general procedures.

Reaction of Diethylamine with Styrene.—Diethylamine (7.3 g, 0.10 mol) was added to 150 ml of nitrogen-degassed cyclohexane in a 12-oz beer bottle. *sec*-Butyllithium (0.32 g, 0.005 mol) was added and allowed to equilibrate for a few minutes at room temperature. Styrene (10.4 g, 0.10 mol) was added, and the mixture was heated at 50° for 23 hr. The solvent was removed by distillation. Distillation of the crude product gave diethylphenethylamine, isolated in a yield of 57%. The infrared spectrum and boiling point were identical with an authentic sample.

Reaction of 1,3-Di(4-azacyclohexyl)propane with Styrene.—1,3-Di(4-azacyclohexyl)propane (21.0 g, 0.10 mol) was added to 150 ml of nitrogen-degassed cyclohexane in a 12-oz beer bottle. *sec*-Butyllithium (0.32 g, 0.005 mol) was added and allowed to equilibrate for a few minutes at room temperature. Styrene (10.4 g, 0.10 mol) was added, and the mixture was heated at 50° for 23 hr.

The reaction mixture was extracted with dilute hydrochloric acid. The aqueous phase was made basic with sodium hydroxide, extracted several times with chloroform, and dried over sodium sulfate. The chloroform was removed by distillation. The product was isolated in a yield of 80%, mp 63–64°.

Anal. Calcd for $C_{29}H_{40}N_2$: C, 83.25; H, 10.05; N, 6.70. Found: C, 83.20; H, 10.16; N, 6.71.

Reaction of Diethylamine with 1,3-Isoprene.—Diethylamine (7.3 g, 0.10 mol) was added to 150 ml of nitrogen-degassed cyclohexane in a 12-oz beer bottle. *sec*-Butyllithium (0.32 g, 0.005 mol) was added and allowed to equilibrate for a few minutes at room temperature. Isoprene (6.8 g, 0.10 mol) was added, and the mixture was heated at 50° for 23 hr. The solvent was removed by distillation. Distillation of the crude product gave 4-diethylamino-2-methyl-2-butene, isolated in a yield of 57%, picrate mp 100–101° (lit.[8] mp 101–102°).

Reaction of Piperidine with Styrene.—Piperidine (8.5 g, 0.10 mol was added to 150 ml of nitrogen-degassed cyclohexane in a 12-oz beer bottle. *sec*-Butyllithium (0.32 g, 0.005 mol) was added and allowed to equilibrate for a few minutes at room temperature. Styrene (10.4 g, 0.10 mol) was added, and the mixture was heated at 50° for 5 hr. The solvent was removed by distillation. Distillation of the crude product gave *N*-phenethylpiperidine, isolated in a yield of 81%. *Anal.* Calcd for $C_{13}H_{19}N$: C, 82.54; H, 10.05; N, 7.41. Found: C, 81.58; H, 10.07; N, 8.58.

Reaction of 1,1-Diphenylethylene with Piperidine.—Piperidine (17.0 g, 0.20 mol) was added to 150 ml of nitrogen-degassed cyclohexane in a 12-oz beer bottle. *sec*-Butyllithium (0.32 g, 0.005 mol) was added and allowed to equilibrate for a few minutes at room temperature. 1,1-Diphenylethylene (26.5 g, 0.10 mol) was added, and the mixture was heated at 50° for 48 hr. The solvent and excess piperidine were removed by distillation. Distillation of the crude product gave *N*-2,2-diphenylethylpiperidine in a yield of 82%. *Anal.* Calcd for $C_{19}H_{23}N$: C, 86.04; H, 8.68; N, 5.28. Found: C, 85.57; H, 8.85; N, 5.71.

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