N-Vinyl as N-H Protecting Group. Synthesis of Cyclic Imines from *N*-Vinyllactams and Organolithium Reagents (1).

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On reaction with organolithium reagents followed by hydrolysis and distillation, *N*-vinylpyrrolidone (**1**) gives five-membered ring imines **3-8**, whereas *N*-vinylcaprolactam (**2**) gives mixtures of seven-membered ring imines and the corresponding ϵ-amino ketones.

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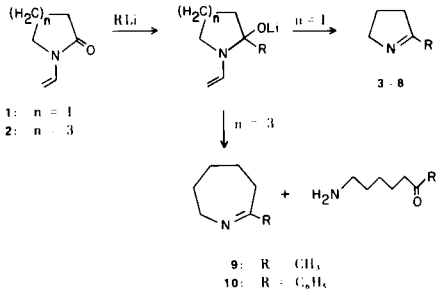
A carbon-carbon bond-forming condensation of pyrrolidone with ethyl nicotinate can be achieved if *N*-vinylpyrrolidone (**1**) is used as starting material instead of pyrrolidone itself (2). We here present another application in which an *N*-vinyl group serves as N-H protecting group, namely the synthesis of cyclic imines from *N*-vinyllactams **1** and **2** and organolithium reagents:



With **1** as starting material, **3-8** were obtained in a pure state after hydrolysis and distillation, but with **2** as starting material, mixtures of imines and amino ketones were obtained. The content of **10** in the distillate was found to increase on repeated distillation, but no pure compound could be isolated in this way. A small amount of **9** was obtained in about 98% purity by preparative glc. Treatment of the products from **2** with benzoyl chloride under Schotten-Baumann reaction conditions gave crystalline *N*-benzoyl derivatives of the amino ketones in good to moderate yields. No *N*-benzoyl derivatives of the imines could be detected in the reaction mixtures.

Table 1

Five-membered Ring Imines Synthesised from *N*-Vinylpyrrolidone

Compound	R	B.p. (a) or m.p.	Yield (%)
3	$-CH_3$	103-105/760	55
4	$-CH(CH_3)_2$	142-143/760	40
5	$-C_4H_9$	84-86/27	71
6	$-C_6H_5$	104-106/5	79
7	3-pyridyl	-	40
8	β-styryl	85.5-87.5°	19

(a) Given in °/mm.

In contrast to our experience of the ring-chain tautomeric behaviour of seven-membered ring imines, most published syntheses of such compounds have been regarded as giving imines free from amino ketones (3-8). An exception is the synthesis of 2-benzyl-4,5,6,7-tetrahydro-3*H*-azepine (6). The pure imino form of the 3,4-dimethoxyphenyl analogue has been obtained by spontaneous crystallization of the distillate (9).

The reaction of Grignard reagents with *N*-vinyllactams seems less promising from a synthetic point of view. The use of butylmagnesium bromide instead of butyllithium resulted in low yields of **5** (15-20%).

In the first published applications of the present synthetic technique, myosmine (**7**) and its 2-pyridyl isomer were synthesised from **1** and pyridyllithium reagents (10).

EXPERIMENTAL

N-Vinylpyrrolidone was purchased from Fluka and was distilled before use. *N*-Vinylcaprolactam was a gift from BASF, Ludwigshafen, Federal Republic of Germany, and was used without purification. The general procedure follows the synthesis of **3**. The other imines were, however, extracted with ether instead of methylene chloride and after drying (sodium sulfate), the ether was evaporated under reduced pressure. Nmr spectra were recorded on a Varian A-60A or a Varian XL-100 instrument, uv spectra on a Beckman DK2 spectrometer, mass spectra on a Varian MAT 311 spectrometer, equipped with a glc inlet system (OV-225 column), and ir spectra on a Perkin-Elmer 257 spectrometer. Melting points are corrected. Elemental analyses were carried out at Alfred Bernhardt, Mikroanalytisches Laboratorium, Elbach über Engelskirchen, Federal Republic of Germany.

3,4-Dihydro-5-methyl-2*H*-pyrrole (**3**).

A solution of **1** (5.0 g., 45 mmoles) in ether (50 ml.) was added during 2 minutes to a stirred ethereal solution (-20°) of methyllithium (1.5 *M*, 50 mmoles) under such cooling that the temperature did not exceed -5°. The reaction mixture was then stirred for 2 minutes at -20° and subsequently poured into 1 *M* hydrochloric acid (70 ml.). After adjustment of *p*H to 1-2 followed by stirring for a couple of minutes, the organic layer was separated and was then extracted with dilute hydrochloric acid. The aqueous layers were combined, then washed once with a little ether. Strong sodium hydroxide solution was added until *p*H 10 was reached and the imine was then extracted with methylene chloride (3 x 30 ml.). The extracts were combined and dried (sodium sulfate) and the solvent was distilled off through a short packed column. The imine was distilled at 103-105° giving

3 in 55% yield, lit. (11) b.p. 103-106°; ^{1}H nmr (deuteriochloroform): δ 3.76 (m, 2H), 2.70-2.30 (m, 2H), 2.15-1.55 (m, (5H).

3,4-Dihydro-5-isopropyl-2*H*-pyrrole (**4**).

A solution of **1** in ether was added to a solution of isopropyllithium in pentane, cooled to -40°, at such a rate that the temperature did not exceed -25° (3 minutes). The mixture was then stirred at -40° for 50 minutes, b.p. 142-143°, lit. (12) b.p. 138°/740 mm, yield, 40%; ^{1}H nmr (deuteriochloroform): δ 3.79 (m, 2H), 2.9-1.5 (5H), 1.16 (d, 6H).

5-Butyl-3,4-dihydro-2*H*-pyrrole (**5**).

The reagents were mixed at -60° to 0° and the mixture was then stirred at 0° for a couple of minutes prior to hydrolysis, b.p. 84-86°/27 mm (71% yield), lit. (13) b.p. 68.5°/19 mm; ^{1}H nmr (deuteriochloroform): δ 3.80 (m, 2H), 2.7-0.7 (13 H).

3,4-Dihydro-5-phenyl-2*H*-pyrrole (**6**).

The reagents were mixed at -30° to -10° and were then allowed to react at approximately -15° for 1 hour. On distillation at 104-106°/5 mm a 79% yield of **6** was obtained, lit. (11) b.p. 245-247°; ^{1}H nmr (deuteriochloroform): δ 8.0-7.2 (m, 2H), 7.5-7.2 (m, 3H), 4.04 (nine lines, 2H, J_1 = 7.3 Hz, J_2 = 2.0 Hz), 2.89 (m, 2H), 1.94 (m, 2H).

3,4-Dihydro-5-(3-pyridyl)-2*H*-pyrrole (myosmine) (**7**).

3-Pyridyllithium was prepared at -70° by adding (30 minutes) a solution of 3-brompyridine (25 mmoles) in ether to a solution of butyllithium (33 mmoles) in ether. The mixture was stirred at -70° for 30 minutes and a solution of **1** (33 mmoles) in ether was then added; the temperature being maintained at -70°. After 2.5 hours, the mixture was allowed to reach -30° during 30 minutes and was then worked up. Purification of the crude product on silica gel using ethyl acetate-methanol (4:1) as solvent gave myosmine in a 40% yield, identified by comparison with an authentic sample (2) (^{1}H nmr).

3,4-Dihydro-5-(2-phenylethenyl)-2*H*-pyrrole (**8**).

Styryllithium was prepared from β-bromostyrene (*cis*/*trans* = 35/65) and lithium containing 2% sodium. Solutions of **1** and styryllithium in ether were mixed at -20° to 0°. After stirring at -20° for 10 minutes followed by the usual work-up, the crude product was purified on alumina (ether as solvent) to give a 19% yield of crystalline **8**. An analytical sample was obtained after two recrystallizations from ether, m.p. 85.5-87.5°; ^{1}H nmr (deuteriochloroform): δ 7.6-7.2 (m, 5H), 7.11 and 6.91 (AB spectrum, 2H, J = 17 Hz), 3.98 (m, 2H), 2.76 (m, 2H), 1.95 (m, 2H). This large coupling constant indicates a *trans* relationship between the two hydrogens. Uv spectrum in ethanol (nm, $\epsilon \cdot 10^{-4}$): 280, 3.1; 228, 1.6; 222, 2,1; 216, 1.9, ir (potassium bromide): 1632 cm^{-1}.

Anal. Calcd. for $C_{12}H_{13}N$: C, 84.17; H, 7.65; N, 8.18. Found: C, 84.07; H, 7.53; N, 8.13.

7-Benzamido-2-heptanone.

A stirred solution of methyllithium (30 mmoles) in ether (22 ml.) was cooled to -20° and a solution of **2** (21 mmoles) in ether (20 ml.) was added dropwise (5 minutes), keeping the temperature at -20°. After stirring for an additional 20 minutes, the cooling bath was removed and the temperature was allowed to rise to -5°. The solution was poured onto ice-hydrochloric acid (4*M*, 20 ml.) and the resulting mixture was stirred for 20 minutes and then washed with ether. Sodium chloride was added as well as sodium hydroxide solution to give *p*H 10. The alkaline aqueous layer was extracted with tetrahydrofuran (2 x 75 ml.). Benzoyl chloride (4.2 g.), followed by sodium hydroxide solution (20 ml., 30%) were added at 0° to the combined tetrahydrofuran layers. The mixture was stirred without cooling for 2 hours and the organic layer was separated, treated with active carbon and then dried (sodium sulfate). After evaporation of the solvent, the crude product was filtered through a short column of silica gel with ethyl acetate as eluant. Crystallization from ethyl acetate-cyclohexane gave a 70% yield of the title compound. An analytical sample was obtained from ether, m.p. 58.5-59.5°. ir (potassium bromide): 1710, 1629 cm^{-1}; ^{1}H nmr (deuteriochloroform): δ 7.9-7.6 (m, 2H), 7.5-7.2 (m, 3H), 6.56 (broad, 1H), 3.40 (q, 2H), 2.40 (t, 2H), 2.11 (s, 3H), 2.0-1.1 (m, 6H). The quartet at δ 3.40 turned into a triplet when N-H was replaced by N-D.

Anal. Calcd. for $C_{14}H_{19}NO_2$: C, 72.07; H, 8.21; N, 6.00. Found: C, 71.99; H, 8.18; N, 5.97.

2-Methyl-4,5,6,7-tetrahydro-3*H*-azepine (**9**).

The imine-amino ketone mixture obtained as above was subjected to preparative glc (10% Carbowas 20 M on Chromosorb W, 190 cm, 90°). The eluted imine, which formed a single peak on glc, was contaminated by approximately 10% (nmr) of the corresponding amino ketone (ir absorption peak at 1710 cm^{-1}). Once repeated preparative glc afforded a sample of the title compound containing about 2% (nmr) of the amino ketone (*N*-CH_3 at δ 2.14); ir (chloroform): 1665 cm^{-1}; ms (m/e, relative intensity): M^+ = 111(18), 96(7), 83(22), 68(24), 42(100), 41(35); ^{1}H nmr (deuteriochloroform): δ 3.65-3.42 (m, 2H), 2.45-2.22 (m, 2H), 2.04 (s, 3H), 1.92-1.20 (m, 6H).

10-Benzamido-5-decanone.

Butyllithium (7.6 mmoles) was allowed to react with **2** (7.2 mmoles) as described above for methyllithium. After work-up and subsequent reaction with benzoyl chloride (10 mmoles) as above, the title compound (63%) was crystallized from ether; m.p. 60-61°; ^{1}H nmr (deuteriochloroform): δ 8.2-7.0 (m, 6H), 3.40 (q, 2H), 2.37 (t, 4H), 1.9-0.6 (m, 13H); ir (potassium bromide): 1702, 1631 cm^{-1}.

Anal. Calcd. for $C_{17}H_{25}NO_2$: C, 74.14; H, 9.15; N, 5.09. Found: C, 74.01; H, 9.00; N, 5.07.

6-Benzamido-1-phenyl-1-hexanone.

Solutions of phenyllithium (0.26 mole) and **2** (0.14 mole) were mixed at -5° to +10° and the mixture was then stirred at -15° for 40 minutes. After work-up, the crude reaction product was treated with benzoyl chloride (0.36 mole) as above. The title compound (59%) was crystallized from ether and showed m.p. 96.5-97°; ^{1}H nmr (deuteriochloroform): 8.1-7.6 (m, 4H), 7.6-7.1 (m, 6H), 6.80 (broad, 1H), 3.45 (q, 2H), 2.95 (t, 2H), 2.0-1.2 (m, 6H); ir (potassium bromide): 1687, 1633 cm^{-1}.

Anal. Calcd. for $C_{19}H_{21}NO_2$: C, 77.27; H, 7.17; N, 4.74. Found: C, 77.26; H, 7.13; N, 4.73.

Attempted Purification of **10** by Distillation.

The crude base gave ir (chloroform) absorption peaks at 1680 (ketone) and 1633 cm^{-1} (imine); the former being approximately 10 times stronger. After the first distillation (125-145°/0.1 mm) it was 3 to 4 times stronger, and after the second one (135-150°/-1.7 mm) it was approximately 50% stronger. Nmr spectrum (deuteriochloroform) of the second distillate showed a multiplet at δ 3.68-3.95 (integral; 12 mm) and a triplet at δ 3.34 (integral: 10 mm) indicating an excess of the imino form.

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Note added in proof:

A paper similar to Spitzner's (10) has recently appeared: J. I. Seeman, *Synthesis*, 498 (1977).