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for the Preparation
of Organic Compounds

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September 2014: The paragraphs above replace the section "Handling and Disposal of Hazardous Chemicals" in the originally published version of this article. The statements above do not supersede any specific hazard caution notes and safety instructions included in the procedure.

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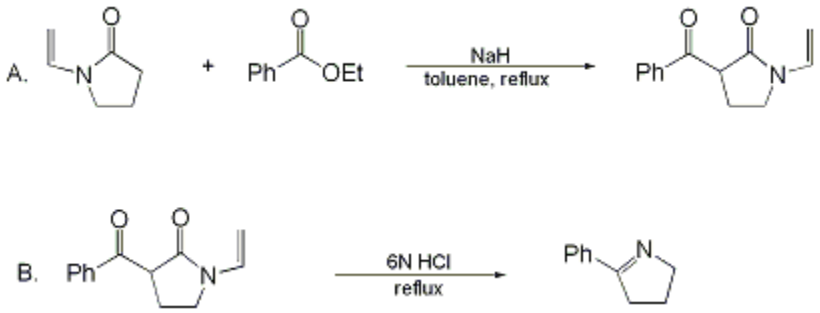
N-VINYLPYRROLIDIN-2-ONE AS A 3-AMINOPROPYL CARBANION EQUIVALENT IN THE SYNTHESIS OF SUBSTITUTED 1-PYRROLINES: 2-PHENYL-1-PYRROLINE

[2H-Pyrrole, 3,4-dihydro-5-phenyl-]



Submitted by Kirk L. Sorgi, Cynthia A. Maryanoff, David F. McComsey, and Bruce E. Maryanoff[1] .
Checked by Christopher Deur and Louis S. Hegedus.

1. Procedure

A. 3-Benzoyl-N-vinylpyrrolidin-2-one . A dry, 2-L, three-necked, round-bottomed flask, equipped with a mechanical stirrer, addition funnel, heating mantle, and reflux condenser, is charged with 26.7 g (0.665 mol) of 60% sodium hydride (NaH, (Note 1)) and 250 mL of dry toluene (Note 2). The stirred suspension is heated at reflux while a mixture of 55.0 g (0.50 mol) of freshly distilled N-vinylpyrrolidin-2-one (Note 3) and 75.0 g (0.50 mol) of ethyl benzoate (Note 4) is slowly added (Note 5). Heating is continued for 10 hr (Note 6). The reaction mixture is cooled to room temperature and the resultant thick slurry is carefully diluted with 250 mL of saturated, aqueous ammonium chloride . The layers are separated and the aqueous layer is extracted again with 250 mL of toluene . The combined organic layers are dried ($MgSO_4$) and concentrated under reduced pressure to afford 108 g (>100%) of crude keto lactam product as an amber oil that may solidify on standing (Note 7).

B. 2-Phenyl-1-pyrroline . A 2-L, three-necked, round-bottomed flask, equipped with a mechanical stirrer, addition funnel, heating mantle, reflux condenser, and a short-path distilling head, is charged with 0.5 L of 6 N hydrochloric acid and heated at reflux; 100 g (0.46 mol) of crude keto lactam is dissolved in 62.5 mL of tetrahydrofuran (THF) and the solution is slowly added, over 1.5-2 hr. Tetrahydrofuran is collected during the addition by use of the short-path distilling head (Note 8). Following the addition, the distilling head is removed and the solution is heated at reflux for 4 hr, cooled to room temperature, filtered through a plug of glass wool, cooled to 0°C, made basic to pH 12 by using aqueous 50% sodium hydroxide , and extracted with methylene chloride (3 × 100 mL). The combined organic layers are dried ($MgSO_4$) and concentrated under reduced pressure to afford 69.2 g of crude product as an amber oil. The residue is distilled at reduced pressure (1-3 mm) and the fraction boiling at 75-85°C is collected to afford 41.0 g (61% yield) of purified product as a clear, colorless oil that solidifies on standing (Note 9).

2. Notes

1. Sodium hydride was a 60% dispersion in mineral oil; 80% or 95% NaH can also be used.
2. Reagent grade toluene should be dried over 4 Å molecular sieves. Anhydrous tetrahydrofuran in SureSeal bottles from the Aldrich Chemical Company, Inc. , can also be used.
3. Higher yields are obtained when freshly distilled N-vinylpyrrolidin-2-one is used.
4. Ethyl benzoate was used as received from the Aldrich Chemical Company, Inc.

5. The addition rate is determined by the rate of hydrogen evolution. Hydrogen evolution ceases before addition of the mixture is complete.
6. A thick precipitate forms at this time.
7. The crude keto lactam is used without further purification. However, the crude solid can be crystallized from warm 2-propanol to yield 68 g of material (63%): mp 66.5-69.5°C; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 2.13-2.37 (m, 1 H), 2.65-2.75 (m, 1 H), 3.42-3.58 (m, 1 H), 3.58-3.74 (m, 1 H), 4.31-4.51 (m, 2 H), 4.57 (dd, 1 H, J = 9.4, 5.2), 7.01 (dd, 1 H, J = 15.9, 9.0, CH vinyl), 7.30-7.63 (m, 3 H), 7.64-7.47 (m, 2 H) ; IR (KBr) cm^{-1}: 1697, 1673, 1635, 1394, 1278, 816 ; MS (FAB) m/z 238 (M^+ + Na), 216 (MH^+), 105 .
8. This high-dilution technique minimizes polymerization. To avoid formation of the brown polymer, the addition must be slow. The submitters recommend adding the keto lactam/THF solution over 1.5-2.0 hr to a vigorously boiling solution of 6 N hydrochloric acid. This addition time leads to high yields of product with minor amounts of dark polymer. It is also important to prevent hydrochloric acid vapors from coming in contact with the keto lactam/THF solution while it is in the addition funnel. This can be accomplished by passing a slow stream of an inert gas over the solution from the top of the addition funnel or by using an addition funnel without a pressure equalizing arm.
9. This material, which yellows on standing, was >95% pure by GLC analysis (DB-5 capillary column, 110°C for 2 min, increase at 30°/min to 290°C). Overall yields should range from 70-75%. The physical properties of 2-phenyl-1-pyrroline are as follows: mp 41.5-44.0°C; ^{1}H NMR ($CDCl_3$, 90 MHz) δ: 1.70-2.10 (m, 2 H), 2.60-2.97 (m, 2 H), 3.80-4.13 (m, 2 H), 7.13-7.47 (m, 3 H), 7.56-7.93 (m, 2 H) ; ^{13}C NMR (100 MHz, $CDCl_3$) δ: 22.41 (CH_2), 34.56 (CH_2), 61.34 (CH_2), 127.36 (CH), 128.12 (CH), 129.96 (CH), 134.40 (C), 172.69 (C=N) ; IR ($CHCl_3$) cm^{-1}: 3061, 2948, 2864, 1616, 1575, 1496, 1447, 1340, 1310, 1049, 991, 961 ; (EI, 70 ev) m/z 145 (M^+), 117, 104, 89, 77, 63, 51 .

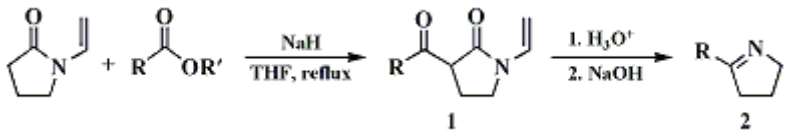
Waste Disposal Information

All toxic materials were disposed of in accordance with "Prudent Practices in the Laboratory"; National Academy Press; Washington, DC, 1995.

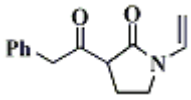
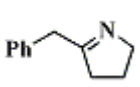
3. Discussion

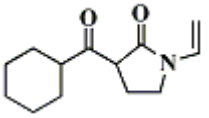
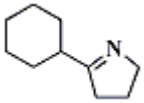
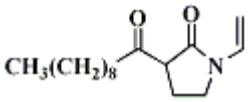
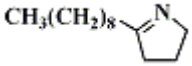
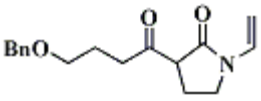
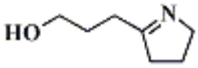
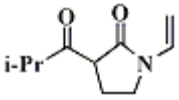
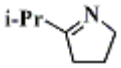
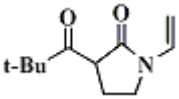
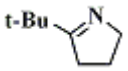
This method for preparing 2-phenyl-1-pyrroline, and assorted 2-substituted 1-pyrrolines, is one of the best currently available, particularly because it reproducibly affords clean materials. Generally, the procedure is amenable to various aromatic esters;[2] [3] [4] it has also been applied successfully to aliphatic esters (Table I).[5] An advantage of this method is the use of readily available, inexpensive N-vinyl-pyrrolidin-2-one as a key starting material. This compound serves effectively as a 3-aminopropyl carbanion equivalent. The method illustrated in this procedure has been extended to include the synthesis of 2,3-disubstituted pyrrolines. Thus, alkylation of the enolate of the intermediate keto lactam, followed by hydrolysis, leads to various disubstituted pyrrolines in good yields (see Table II).[5]

TABLE I
PREPARATION OF 2-ALKYL-1-PYRROLINES



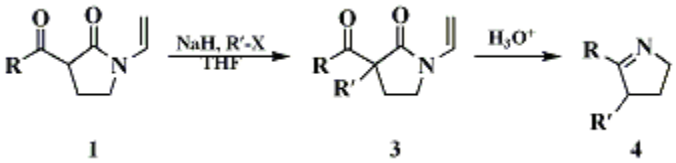
1 2

Entry	Ester	1	Yield **1** (%)[a]	2	Yield **2** (%)[b]
1	$PhCH_2CO_2Et$		96 [c]		66

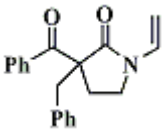
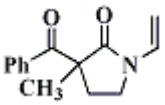
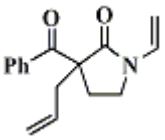
2	c-$C_6H_{11}CO_2CH_3$		99		73
3	$CH_3(CH_2)_8CO_2CH_3$		99		81
4	$BnO(CH_2)_3CO_2CH_3$		96		95 [d]
5	i-$PrCO_2CH_3$		99		98
6	t-$BuCO_2CH_3$		99		98

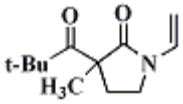
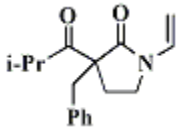
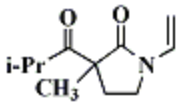
a) Crude yield. b) Isolated purified yield from N-vinylpyrrolidin-2-one. c) Two equiv of NaH were used.
d) Benzyl group was removed during the hydrolysis.

TABLE II
PREPARATION OF 2,3-DISUBSTITUTED-1-PYRROLINES



1 3 4

Entry	R	R'-X	**3**	Yield **3** (%)[a]
1	Ph	$PhCH_2Br$		99 (70)
2	Ph	CH_3I		99
3		$PhH_2C{=}CHCH_2Br$		92
4	t-Bu	CH_3I		97

					t-Bu- Cl
5	i-Pr	$PhCH_2Br$		99	i-Pr-
5	i-Pr	CH_3I		77	i-Pr- CH

a) Crude yield. Bracketed yield is after purification by crystallization. b) Isolated purified yield fr
c) Yield from purified **3**.

Other methods are available for the synthesis of 2-substituted 1-pyrrolines. A comparison study of their preparation from organolithium reagents and N-vinyl-pyrrolidin-2-one has been reported.[6] Additions of phenyllithium to N-acylpyrrolidin-2-one [7] and phenyl Grignard reagents to a methyl imidate derived from 2-pyrrolidinone [8] are also useful (although the latter process requires a strong methylating agent). Two Friedel-Crafts methods[9] [10] [11] and the reaction of aroyl chlorides with 2-pyrrolidinone [12] have been described. There is also a useful procedure, similar to the one presented here, that employs N-trimethylsilylpyrrolidin-2-one.[13] [14]

2-Phenyl-1-pyrroline is useful for various purposes.[15] [16,17] In particular, its reduction product, 2-phenylpyrrolidine, is important in the synthesis of pyrroloisoquinoline antidepressants,[4,18] [19] [20] and can be a starting point in alkaloid synthesis.[21] [22] The overall reaction sequence described here has been used to prepare nicotine derivatives such as myosmine.[2,3]

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Appendix
Chemical Abstracts Nomenclature (Collective Index Number); (Registry Number)

N-Vinyl-2-pyrrolin-2-one:
2-Pyrrolidinone, 1-vinyl-; 2-Pyrrolidinone, 1-ethenyl- (9); (88-12-0)

2-Phenyl-1-pyrroline:
1-Pyrroline, 2-phenyl- (8);
2H-Pyrrole, 3,4-dihydro-5-phenyl- (9); (700-91-4)

3-Benzoyl-N-vinylpyrrolidin-2-one:
2-Pyrrolidinone, 3-benzoyl-1-ethenyl-, (±)- (12); (125330-80-5)

Sodium hydride (8,9); (7646-69-7)

Ethyl benzoate:
Benzoic acid, ethyl ester (8,9); (93-89-0)