Pergamon

Tetrahedron Letters 42 (2001) 6101–6104

TETRAHEDRON LETTERS

Easy one-pot access to substituted 2-phenylpyrrolines from 2-pyrrolidinone

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Received 5 June 2001; revised 2 July 2001; accepted 4 July 2001

Abstract—An easy access to 2-aryl pyrrolidines is the reduction, stereospecific or not, of the corresponding 2-aryl-pyrroline (5-aryl-3,4-dihydro-2*H*-pyrrole). Preparation of the latter has been carried out from 2-pyrrolidinone using an easy one-pot two-step method for the first time.

Substituted 2-phenylpyrrolidines are key intermediates for the preparation of tricyclic systems such as pyrrolo[2,1-*a*]isoquinolines which exhibit significant pharmacological activities.[1]

Several synthetic ways, proposed in the literature, allow these compounds to be obtained and can be classified in two groups: multi-steps stereoselective methods[2] and shorter racemic ways.[1,3,4] Generally, the desired enantiomer, sometimes present in moderate ee, has to be isolated from the mixture of isomers.

Buchwald's method,[5] based on a stereospecific catalytic hydrogenation of a 2-aryl-pyrroline (5-aryl-3,4-dihydro-2*H*-pyrrole) **1**, appeared to be the most accurate for the preparation of pure (*R*)- or (*S*)-2-aryl-pyrrolidine **2**. The ee values reported are so high (generally equal to 99%) that the mixture of enantiomers obtained may be used without further separation (Scheme 1).

Therefore, we decided to investigate the general preparation of substituted 2-phenyl pyrrolines **1**, starting material for Buchwald's reduction to the pyrrolidines **2**. One method starting from *N*-vinyl-pyrrolidinone has been described to obtain a pyrroline substituted either with a phenyl[1] or a 3-pyridyl[6] group, but we were not able to reproduce the results published.[1]

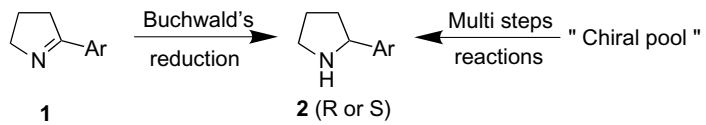
A second approach consists of the addition of aryl lithium or magnesium bromide on 2-pyrrolidinones which necessitates the protection of the nitrogen atom. Generally, the addition leads to the opening of the ring[7] and a second deprotection–cyclization step in basic media was required.

Fowler et al.[8] proposed the reduction of the addition products with $LiAlH_4$ which leads directly to the expected pyrrolidine. In our case, a deprotection step has to be added to this method in order to obtain later the *N*-unsubstituted pyrrolidine (Scheme 2).

Our strategy is based on the transformation of the starting lactam into a pyrroline bearing a leaving group which acts as a protecting group in a first step, but allows the formation of the double bond by spontaneous deprotection.

A first attempt had been described by Etienne and Correia.[3] The pyrrolidinone was *O*-methylated with moderate yields using dimethyl sulfate in refluxing benzene and reacted, after purification, with phenylmagnesium bromide in order to obtain 2-phenyl-pyrroline.

We decided to improve this method and, at the same time, to avoid the use of dimethyl sulfate and benzene.



Scheme 1.

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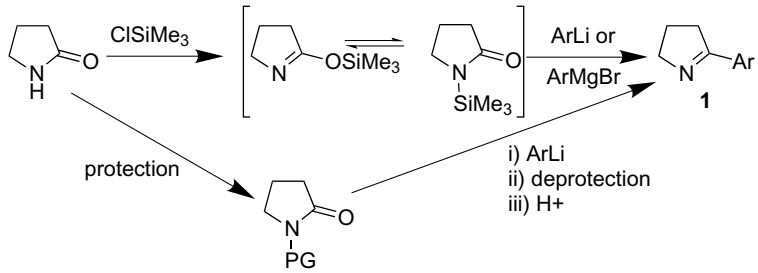


Scheme 2.

We needed a reagent able to react specifically with the oxygen atom leading to an intermediate compatible with the use of an organometallic reagent in a second step.

Blocking the lactam with a trimethylsilyl group, predominantly located on the nitrogen atom, allows us to have a better leaving group than the methoxy group and also a group compatible with the use of organometallic reagents. The reaction can be run as a one-pot procedure since the silylated intermediate can be added without purification to the organometallic derivative. The results are given in Table 1. Silylation of pyrrolidinone leads to two different isomers probably in equilibrium (see Scheme 2) and ^{1}H NMR confirms that this step was quantitative. The purification of this intermediate can be achieved by distillation but does not improve significantly the yields of pyrroline **1**, although only the *N*-substituted pyrrolidinone has been detected and identified by ^{1}H NMR (data identical to those described in Ref. 11) and NOESY experiments, which is in agreement with previous ^{13}C and ^{15}N NMR[9,10] studies.

We must note that during our investigations we realized that this strategy had been previously used but exclusively for the preparation of 2-alkyl-pyrrolines and analogues.[11,12] The authors[11] claimed that the use of Grignard reagents could lead to the expected pyrroline in poor yields due to a side reaction (apparently Grignard reagent attacks the silyllactam at silicon) which is not in agreement with our results. Nevertheless, we observed that the results obtained with Grignard reagents were much less reproducible than those using substituted phenyl lithium ones. This may be an explanation for our divergences. On the other hand, Grignard reagents cannot be used for the preparation of bromo- or iodophenyl pyrrolines. Only substituted biphenyls have been observed in appreciable amounts.

This easy one-pot procedure provides other advantages. The pyrrolines **2** obtained do not need to be further purified and are easily collected, after the hydrolysis of the crude reaction mixture with 1N HCl, by filtration or by extraction with ether from the aqueous basified phase. Of course, we do not need to follow a protection–deprotection procedure and all the reagents used are readily accessible and easy to handle. On the other hand, the great number of bromobenzene derivatives commercially available makes the method really attractive.

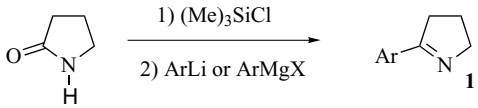
We must underline the fact that, to the best of our knowledge, no substituted 2-aryl-pyrrolines are described in the literature following a related method since generally only the phenyl group is required.

In summary, we described here an alternative, easy to handle one-pot method to prepare substituted 2-arylpyrrolines. These compounds are easily obtained as pure solids (or oils for 2-phenyl and 2-(4-trimethylsilyl)-phenyl-pyrrolines) and can be directly reduced to the expected pyrrolidines either in a racemic mixture or with high ee using Buchwald's method.

Experimental

Typical procedure for the preparation of 2-aryl-pyrrolines 1a–i. To a mixture of 2-pyrrolidinone (42.4 mmol) and triethylamine (44.5 mmol) in diethyl ether was added trimethylsilyl chloride (44.5 mmol) at 0°C under argon.

Table 1. Yields of pyrrolines **1** from 2-pyrrolidinone



	Structure of Ar	1 equiv. of ArMgBr (%)	1 equiv. of ArLi (%)
1a	Phenyl	90	
1b	3-Chloro-phenyl	35	34
1c	4-Chloro-phenyl	45	
1d	4-Methoxy-phenyl	47	
1e	3-Bromo-phenyl		24
1f	4-Bromo-phenyl		45
1g	4-Iodo-phenyl		50
1h	4-Trimethylsilyl-phenyl		41
1i	2-Thienyl		25

The reaction mixture was refluxed for 30 min, cooled at room temperature, and filtrated. A solution of Grignard reagent or aryl lithium (42.4 mmol) was added to the filtrate at room temperature or at −30°C for aryl lithium and allowed to warm to room temperature. The reaction mixture was refluxed for 3 h and then quenched with 1N hydrochloric acid. The aqueous solution was extracted with diethyl ether and then made basic with 10% sodium hydroxide. The basic phase was filtered off in order to collect the pure pyrroline or extracted with diethyl ether, dried over magnesium sulfate and concentrated under vacuum when a Grignard reagent is used.

Product Name	Physical data	^{1}H NMR (250 MHz, $CDCl_3$)	^{13}C NMR (62.5 MHz, $CDCl_3$)
1a 2-Phenylpyrroline	IR: $\nu_{CN}=1615$ cm^{-1}	7.82 (m, 2H)	173.08, 134.44,
		7.37 (m, 3H)	130.10, 128.22,
	Oil	4.09 (m, 2H)	127.42, 61.32, 34.73,
		2.93 (m, 2H)	22.48
		2.04 (m, 2H)	
1b 2-(3-Chloro)phenylpyrroline	IR: $\nu_{CN}=1619$ cm^{-1}	7.83 (s, 1H)	172.09, 136.32,
		7.70 (d, 1H, $J=7.4$)	134.48, 130.21,
	Mp 54°C	7.37 (m, 1H)	129.63, 127.69,
		7.34 (d, 1H, $J=7.4$)	125.67, 61.55, 34.88,
		4.09 (m, 2H)	22.62
		2.91 (m, 2H)	
		2.04 (m, 2H)	
1c 2-(4-2-(4-Chloro)-phenylpyrroline	IR: $\nu_{CN}=1622$ cm^{-1}	7.78 (d, 2H, $J=8.5$)	172.06, 136.22,
		7.38 (d, 2H, $J=8.5$)	132.99, 128.81,
	Mp 65–66°C	4.07 (m, 2H)	128.52, 61.49, 34.78,
		2.93 (m, 2H)	22.61
		2.06 (t, 2H)	
1d 2-(4-Methoxy)phenylpyrroline	IR: $\nu_{CN}=1603$ cm^{-1}	7.78 (d, 2H, $J=8.7$)	172.44, 161.17,
		6.91 (d, 2H, J = 8.7)	129.05, 127.37,
	Mp 74°C	4.02 (m, 2H)	113.59, 61.19, 55.16,
		3.83 (s, 3H)	34.71, 22.60
		2.90 (m, 2H)	
		2.01 (m, 2H)	
1e 2-(3-Bromo)phenylpyrroline	IR: $\nu_{CN}=1618$ cm^{-1}	8.00 (s, 1H)	171.98, 136.62,
		7.75 (d, 1H, $J=8.0$)	133.13, 130.61,
	Mp 49–50°C	7.55 (d, 1H, $J=7.8$)	129.91, 126.11,
		7.27 (dd, 1H, $J=7.8$, $J=7.9$)	122.64, 61.59, 34.86, 22.66
		4.05 (m, 2H)	
		2.91 (m, 2H)	
		2.05 (m, 2H)	
1f 2-(4-Bromo)phenylpyrroline	IR: $\nu_{CN}=1623$ cm^{-1}	7.71 (d, 2H, $J=8.5$)	172.04, 135.51,
		7.54 (d, 2H, $J=8.5$)	131.55, 129.08,
	Mp 87°C	4.05 (m, 2H)	124.69, 61.61, 34.79,
		2.92 (m, 2H)	22.67
		2.05 (m, 2H)	
1g 2-(4-Iodo)phenylpyrroline	IR: $\nu_{CN}=1608$ cm^{-1}	7.75 (d, 2H, $J=8.4$)	172.40, 137.56,
		7.56 (d, 2H, $J=8.4$)	134.04, 129.17, 96.85,
	Mp 99°C	4.05 (m, 2H)	61.62, 34.74, 22.66
		2.91 (m, 2H)	
		2.04 (m, 2H)	
1h 2-(4-Trimethylsilyl)-phenylpyrroline	IR: $\nu_{CN}=1614$ cm^{-1}	7.81 (d, 2H, $J=7.9$)	173.36, 143.35,
		7.56 (d, 2H, $J=7.9$)	133.37, 126.90,
	Oil	4.07 (m, 2H)	126.72, 61.53, 34.89,
		2.95 (m, 2H)	22.63, −1.24
		2.03 (m, 2H)	
		0.28 (s, 9H)	
1i 2-(2-Thienyl)pyrroline	IR: $\nu_{CN}=1609$ cm^{-1}	7.40 (d, 1H, $J=5.0$)	167.87, 139.64,
		7.31 (d, 1H, $J=3.7$)	128.98, 128.90,
	Mp 52°C	7.06 (dd, 1H, $J=3.7$, $J=5.0$)	127.37, 61.28, 35.59, 23.01
		4.03 (m, 2H)	
		2.93 (m, 2H)	
		2.04 (m, 2H)	

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