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A facile synthesis of 3-alkoxy and 3-amino pyrroles

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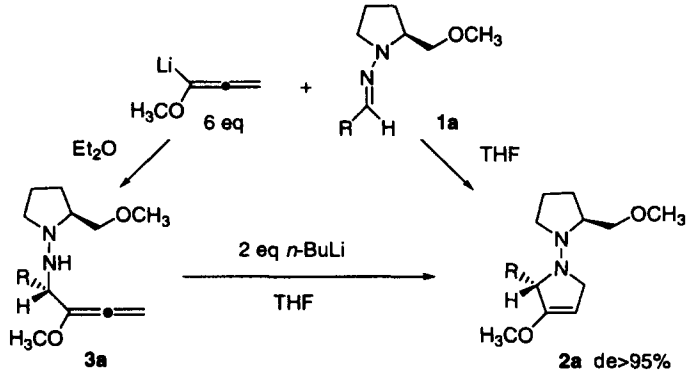
Abstract

N-Amino-3-methoxy-3-pyrrolines **2** obtained from the reaction of 1-lithio methoxyallene with arylhydrazones may be converted to either 3-methoxy pyrroles **6** or 3-amino pyrroles **7** by treatment with *m*-chloroperbenzoic acid or 0.25 M HCl, respectively.

We recently reported that the lithio-derivative of methoxyallene reacted with the SAMP-hydrazones **1a** to afford 3-pyrrolinohydrazines **2a**.[1] This cyclisation was easily accomplished in one step for arylhydrazones, or in two steps for alkyl and arylhydrazones (Scheme 1).



Scheme 1.

In order to extend the scope and synthetic utility of this approach, the reactions of other hydrazones under similar conditions have been studied. Dimethylhydrazones, pyrrolydinyl hydrazones and morpholinyl hydrazones were easily synthesised from aryl and alkyl aldehydes and commercially available hydrazines. The condensation reaction was then performed under the conditions employed previously,[1] using 6 equiv. of organometallic reagent in THF. The cyclisation of aryl hydrazones proved more difficult

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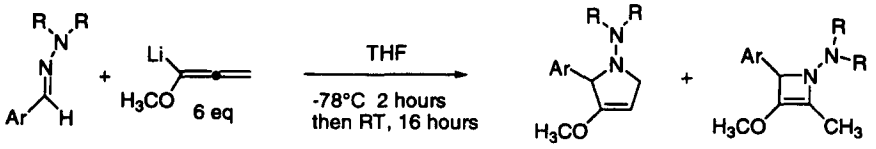
than that of the previously reported SAMP-hydrazones. Addition at –78°C of the organometallic reagent afforded the desired cyclised products after warming to room temperature (rt) for several hours (–20°C in the case of **1a**). The 3-pyrrolinohydrazines **2b–d** were not the sole reaction products, however, and obtention of the four-membered cycles **4b–d** was also observed (Scheme 2). The ratio of four- to five-membered ring formation was found to depend on the nature of the substituents on the terminal nitrogen atom. Formation of the four-membered rings was favoured by *N,N*-dimethyl and piperidinyl hydrazones over their morpholinyl analogues; in this latter case, formation of the four-membered ring may be suppressed by performing the reaction at 50°C (see Table 1).



1b : R = CH_3 **2b** **4b**

1c : R, R = —$(CH_2)_5$— **2c** **4c**

1d : R, R = —$(CH_2)_2$—O—$(CH_2)_2$— **2d** **4d**

Scheme 2.

In contrast, the corresponding alkylhydrazones (R=propyl, isopropyl) failed to yield any cyclised product. Neither direct cyclisation in THF nor cyclisation of the allenic hydrazines **3b–d** resulting from reaction in diethyl ether of 1-lithio methoxyallene with hydrazones proved successful.

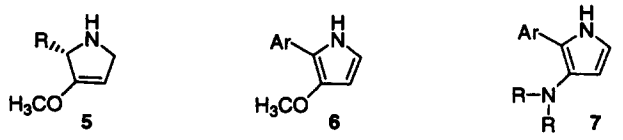
This approach has provided a route to diversely substituted 3-pyrrolinyl hydrazines **2**. In the case of the SAMP-series, 3-pyrrolines **5** may be obtained as a single enantiomer via hydrogenolysis of these 3-

Table 1

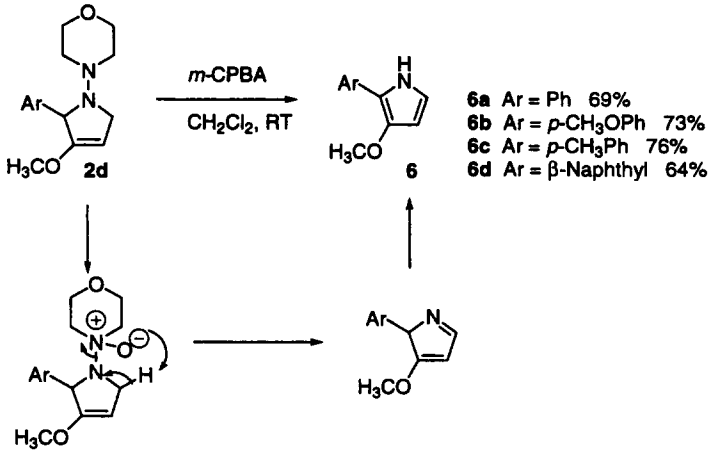
Starting hydrazone		Reaction conditions		Reaction product	
R,R	Ar	Temperature	Time	2 (yield%)	4 (yield%)
Me **1b**	**1ba** Ph	RT	16h	**2ba** 53	**4ba** 22
		50°C	6h	46	26
	1bb *p*-MePh	RT	16h	**2bb** 45	**4bb** 35
	1bc *p*-MeOPh	RT	16h	**2bc** 35	**4bc** 38
	1bd β-naphthyl	RT	16h	**2bd** 77	-
-$(CH_2)_5$- piperidino **1c**	**1ca** Ph	RT	16h	**2ca** 46	**4ca** 28
		RT	96h	46	27
	1cb *p*-MeOPh	RT	16h	**2cb** 38	**4cb** 38
	1cc β-naphthyl	RT	16h	**2cc** 78	**4cc** 4
-$(CH_2)_2O(CH_2)_2$- morpholino **1d**	**1da** Ph	RT	16h	**2da** 64	**4da** 11
		50°C	6h	74	-
	1db *p*-MeOPh	50°C	6h	**2db** 76	-
	1dc β-naphthyl	RT	16h	**2dc** 60	**4dc** 13
		50°C	6h	78	-
	1dd *p*-MePh	50°C	6h	**2dd** 78	-

In series b and d, the products 2 and 4 are separated by SG-Flash chromatography. The yields correspond to quantities of isolated pure compounds. In sery 1c, the same separation was not possible ; the yields are based on the integration of the ^1H NMR spectra and on the quantity of the purified mixture of 2 and 4.

pyrrolinyl hydrazines **2**.[1] We wish now to report the transformation of the same compounds into the pyrroles **6** and **7**. Although a plethora of methods are available for the preparation of pyrroles, this work most closely resembles those routes in which the final step is conversion of a 3-pyrroline into a pyrrole.[2] The advantage of this new method is in allowing the synthesis of pyrroles functionalised with electrodonating group in the 3-position, for which relatively few examples exist in the literature.[3]

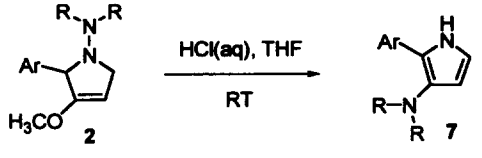


The first transformation was run with the *N*-morpholino-3-pyrrolines **2d** which were obtained with good yields in a single step (Table 1). Treatment of *N*-morpholino-3-pyrroline **2d** with *m*-CPBA in dichloromethane at 25°C afforded the pyrrole **6** in good yield (Scheme 3). This reaction is thought to involve a Cope elimination of an *N*-oxide followed by tautomerisation of the heterocycle.[4] It is worth noting that no reaction was observed when H_2O_2 was used in place of *m*-CPBA.



Scheme 3.

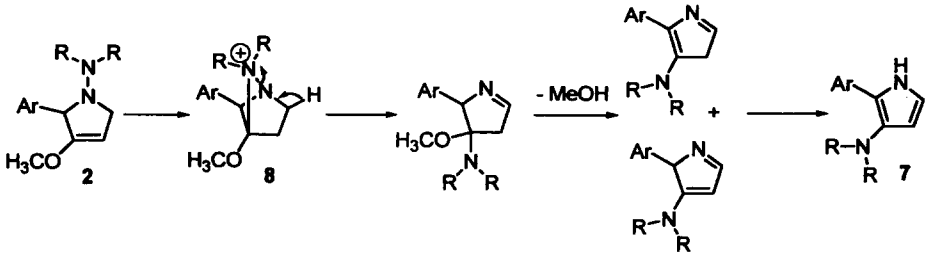
On the other hand, treatment of the compounds **2** with dilute HCl (0.25 M) in THF (1:4) resulted in the somewhat surprising transformation of **2** into **7**. The 1,3-migration of the external amino group occurs quantitatively regardless of the nature of the substituents: SMP, dimethylamino, piperidino or morpholino (Scheme 4).



Scheme 4.

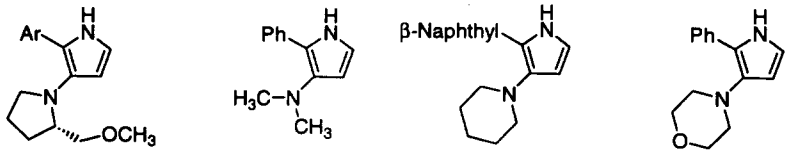
The mechanism of this migration probably involves the formation of a bridged ammonium species **8**[5] followed by sequential β-elimination and elimination of methanol to give **7** (Scheme 5).

Examples of 3-amino pyrroles obtained are shown (Scheme 6). With **2a**, **2b** and **2d** the corresponding 3-amino pyrrole was obtained cleanly in quantitative yield. In the case of **2c**, where separation of the four- and five-membered cycles **2ca** and **4ca** proved problematic, the reaction was performed on a mixture of the two where R=β-naphthyl. However, the 3-amino pyrrole **7cc** was the only product isolated from the



Scheme 5.

reaction, suggesting that the four-membered cycle **4cc** is degraded under the reaction conditions. The 3-amino pyrroles **7** are relatively unstable to chromatography but the crude product presents a ≥95% purity as shown by ^{1}H and ^{13}C NMR spectroscopy.



7aa Ar=Ph
7ab Ar=*p*-CH_3Ph

7ba **7cc** **7da**

Scheme 6.

In conclusion, a two step preparation of 3-methoxy and 3-dialkylamino pyrroles has been developed. The method extends the synthetic utility of alkoxyallenes, with the potential for the scope of this reaction to be further applied to other alkoxy and amino groups.

Acknowledgements

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