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A versatile synthesis of polysubstituted pyrroles

Bharat Lagu,* Meng Pan and Michael P. Wachter

The R. W. Johnson Pharmaceutical Research Institute, Route 202, PO Box 300, Raritan, NJ 08869, USA

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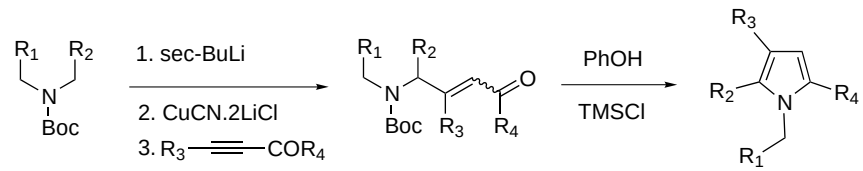
Abstract—The aldol products formed by the reaction between α-(*N*-benzyl or *N*-Cbz)amino aldehydes and lithium enolates of various ketones, were subjected to hydrogenolysis to give polysubstituted pyrroles in good yields (50–91%). The scope and limitations of this methodology are explored.

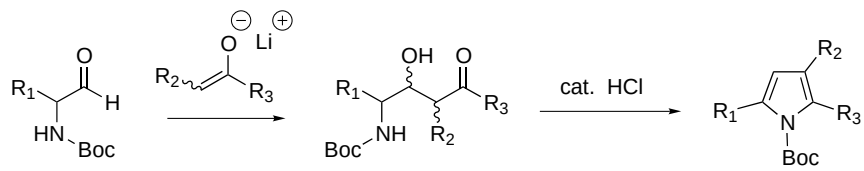
Pyrroles have been used as a pharmacophore by many research laboratories, which has led to development of new methodologies for the synthesis of pyrroles.[1] During the course of a program targeted towards the synthesis of anti-inflammatory agents, an easy access to polyalkylated pyrroles, which did not bear electron-withdrawing groups, was warranted. A majority of the known synthetic routes were found to be of limited utility as they either lead to pyrroles bearing electron-withdrawing groups or were not amenable for incorporation of a variety of alkyl or aryl substituents on the pyrrole ring.[2,3]

A novel synthesis of polysubstituted pyrroles was reported recently by Dieter and Yu via conjugate addition of α-amino-alkylcuprates to alkynyl ketones followed by amine deprotection and cyclization (Eq. (1)).[4] However, the need to synthesize alkynyl ketones, the possibility of obtaining regioisomers when R_1 and R_2 are unsymmetrical, and the inability to synthesize 2,5-diaryl pyrroles were thought to be limitations of this synthetic route.

We were intrigued by the elegant synthesis of pyrroles reported by Cushman and coworkers which utilizes aldol products formed by the reaction between (*N*-Boc)-α-amino aldehydes and ketones (Eq. (2)).[5] Some noteworthy features of this synthetic route are the ready availability of the starting materials, mild conditions and the number of substituents at R_1, R_2 and R_3 that can be accessed. However, the yields were rather modest (5–40%) and in all cases pyrroles with alkyl substituents on the nitrogen could not be accessed by this route.[6] A possible explanation for the low yields could be a rapid polymerization of the resulting pyrroles under the acidic conditions employed. We reasoned that if one could replace the *tert*-butoxycarbonyl group on the nitrogen with another protecting group that can be removed under relatively neutral conditions, the yields of pyrroles could be improved and allow for a number of substituents to be introduced on the pyrrole nitrogen.



(1)



(2)

* Corresponding author. Tel.: 908-704-4291; fax: 908-526-6469; e-mail: blagu@prius.jnj.com

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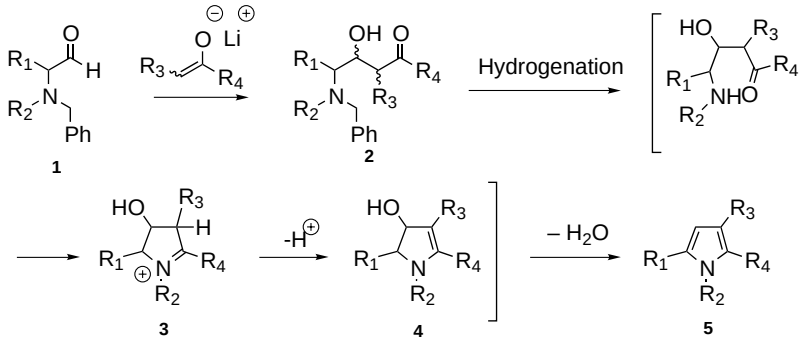
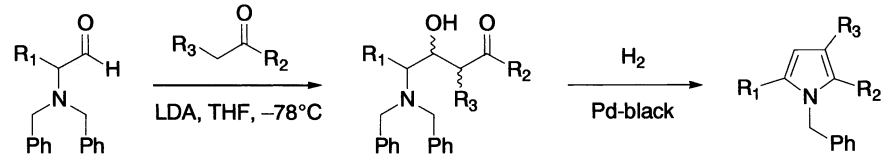


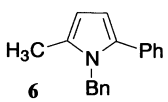
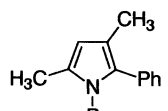
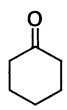
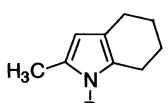
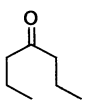
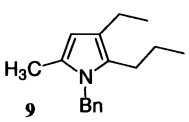
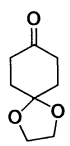
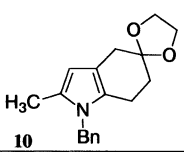
Scheme 1.

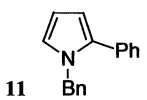
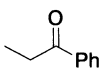
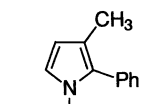
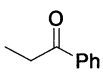
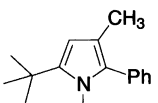
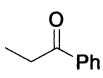
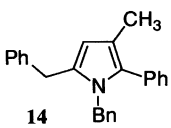
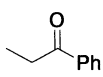
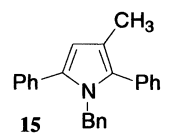
A benzyl group was considered as a potential replacement for the *tert*-butoxycarbonyl group on the nitrogen of the α-amino aldehydes to be used in the aldol reactions. Aldol reactions of α-(*N*,*N*-dibenzyl)amino aldehydes or α-(*N*,*N*-dibenzyl)amino ketones have been reported by a number of groups.[7] We speculated that deprotection of the benzyl groups could lead to formation of an iminium ion (**3**) which could undergo a deprotonation to provide an enamine (**4**) (Scheme 1). The enamine can then undergo dehydration to yield pyrrole (**5**).

The required α-(*N*,*N*-dibenzyl)amino aldehydes were synthesized by Swern oxidation of the β-(*N*,*N*-dibenzyl)amino alcohols which were obtained from the commercially available β-amino alcohols.[8] The α-(*N*,*N*-dibenzyl)amino aldehydes were reacted with lithium enolates of various ketones at −78°C to obtain the corresponding aldol products in 70–90% yield. The aldol products, when subjected to standard hydrogenation conditions (1 atm of H_2 in the presence of palladium black in methanol, 1–4 h), gave the corresponding pyrroles **6**–**15** in good yields (Table 1).[9,10] It is evident

Table 1.



R_1	Ketone	Pyrrole	%Yield*
Me		 **6**	91 (74)
Me		 **7**	75 (66)
Me		 **8**	52
Me		 **9**	63
Me		 **10**	50

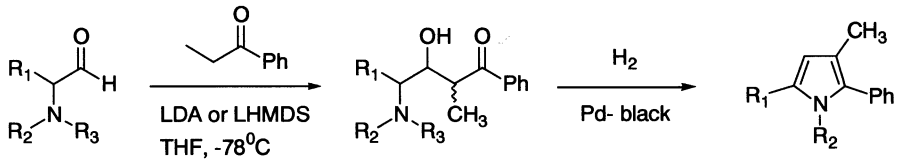
R_1	Ketone	Pyrrole	%Yield*
H		 **11**	(69)
H		 **12**	75 (66)
t-Bu		 **13**	78
Bn		 **14**	(81)
Ph		 **15**	92

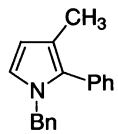
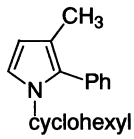
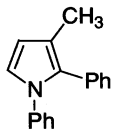
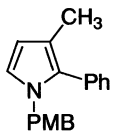
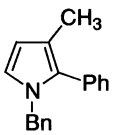
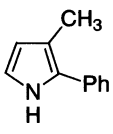
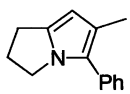
* Yields refer to the formation of pyrroles from the aldol products and were determined by ^{1}H NMR using internal standard (N-*Boc*-Pyrrole). Yields in parenthesis are for the products purified by column or preparative silica gel chromatography.

that various substituents, including the sterically demanding *tert*-butyl group, are tolerated at the 2-, 3- and 5-positions of the pyrroles. The synthetic methodology is flexible enough to yield a variety of substituent combinations and 1,2-di-, 1,2,3-tri-, 1,2,5-tri- and 1,2,3,5-tetra-substituted pyrroles can be synthesized. Pyrroles fused to carbocyclic rings (**8** and **10**) can also be accessed using this synthetic route.

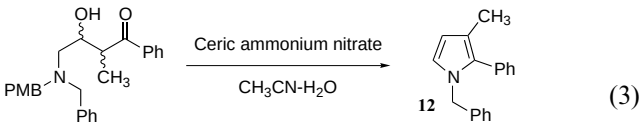
The methodology described herein allows for the introduction of a number of alkyl and aryl substituents on the nitrogen of pyrroles (Table 2, **12** and **16–18**) that cannot be readily synthesized using known procedures. In addition, we were able to exploit the differences in the rates of hydrogenation between a *p*-methoxybenzyl group and a benzyl group (**18**) or between a carbobenzyloxy group and a benzyl group[11] (**12**, Table 2, entry 5) to achieve chemoselective removal of one of the protecting groups. In contrast, when a chemoselective removal of the *p*-methoxybenzyl group was attempted by ceric ammonium nitrate (Eq. (3)),[12] formation of pyrrole **12** was evident only by mass spectroscopy and thin layer chromatography of the reaction mixture. Attempts to isolate the pyrrole were unsuccessful. This result highlights the mild conditions reported in this letter. Pyrrole without a substituent on the nitrogen (**19**) could not be synthesized by the methodology. When *N*-benzyl prolinal was used as the α-amino aldehyde (entry 7), 6-methyl-5-phenyl-2,3-dihydro-1*H*-pyrrolizine (**20**) was formed in 52% isolated yield.

Table 2.



Entry	R_1	R_2	R_3	Pyrrole	% Yield
1	H	Bn	Bn	 **12**	75 (66)
2	H	Cyclohexyl	Bn	 **16**	92
3	H	Ph	Bn	 **17**	86
4	H	(4-OMe)-Bn	Bn	 **18**	62
5	H	Bn	Cbz	 **12**	80
6	H	H	Cbz	 **19**	No Pdt.
7		-$(CH_2)_3$-	Bn	 **20**	(52)

* Yield by ^{1}H NMR with internal standard (N-*Boc*-Pyrrole). Yield in parenthesis is for the product purified by column or preparative silica gel chromatography.



(3)

Observed by mass spectroscopy and TLC. Decomposed during work-up

A brief survey of other hydrogenation conditions revealed that palladium black can be replaced with 10% Pd–C or $Pd(OH)_2$ as catalysts for the removal of the benzyl group. The pH of the reaction mixture under standard hydrogenation conditions was around 7. Addition of a trace of acetic acid (<5 μL) shortened the reaction time significantly while the addition of K_2CO_3 was found to hinder the rate of debenzylation. Pyrroles can also be obtained in comparable yields under transfer hydrogenation conditions with ammonium formate,[13] cyclohexadiene[14] or formic acid[15] as the hydrogen donors.

The possible limitation of the methodology described herein could be that the presence of certain functional groups (e.g. mercaptans, thioethers, halogens or nitro group) will not be tolerated due to possible poisoning of the catalyst, dehalogenation or reduction under the hydrogenation conditions.

Thus, a versatile synthesis of polysubstituted pyrroles was accomplished from the aldol product of a reaction between a suitably protected aldehyde and an enolate. The salient features of the synthetic methodology are: (1) the flexibility to synthesize pyrroles with various substituents at the 1-, 2-, 3-, and 5-positions; (2) a wide selection of substituents that can be accessed from commercially available ketones and amino acids; and (3) use of mild reaction conditions. Further modifications of this methodology and applications to biologically important compounds are currently under investigation.

Acknowledgements

The authors thank Dr. William Murray for his support.

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6. Intermediates similar to the aldol products (i.e. γ-acetamido-β-hydroxy ketones) have been synthesized from isoxazolines and were converted into 1-acetyl-2-aryl pyrroles. See: (a) Ghabrial, S. S.; Thomsen, I.; Torssell, K. B. G. *Acta Chem. Scand. Ser. B* **1987**, *41*, 426–434; (b) Mukerji, S. K.; Sharma, K. K.; Torssell, K. B. G. *Tetrahedron* **1983**, *39*, 2231–2235.
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9. The polysubstituted pyrroles were prone to polymerization as evidenced by a change in the appearance of the purified products over time (colorless oil turning pink in a few hours).[3c] An internal standard was used to estimate the yields in an accurate manner.
10. Synthesis of **17** (typical procedure): To a cold solution (ice bath) of 4-(benzylphenylamino)-3-hydroxy-2-methyl-1-phenylbutan-1-one (50 mg, 0.14 mmol) in 5 mL CD_3OD was added Pd black (40 mg) and a balloon filled with H_2 was placed on top of the flask. After about 2 h, the catalyst formed clumps and TLC (10% EtOAc/Hex) and ^1H NMR of the supernatant solution indicated that the reaction was complete. Then *tert*-butyl-1-pyrrolecarboxylate (23.3 μL, 0.14 mmol) was added and the reaction mixture was stirred for 5 min. Yield was determined based on integration of pyrrole peaks of the product and the internal standard between 5.8 and 7.0 ppm in ^1H NMR.
11. For selective deprotection of a benzyl ether in the presence of a PMB ether, see: Horita, K.; Yoshioka, T.; Tanaka, T.; Oikawa, Y.; Yonemitsu, O. *Tetrahedron* **1986**, *42*, 3021–3028.
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