A Facile Non-Oxidative Method for Synthesizing 1,3-Disubstituted Pyrroles from Pyrrolidine and Aldehydes

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Abstract: Reactions of pyrrolidine with two equivalents of aldehydes without any catalyst in a pressurized vessel at 140–200 °C yielded 1,3-disubstituted pyrroles. □-Branched aldehydes gave fairly good yields of the corresponding products by this method, which provides a facile non-oxidative procedure for synthesizing 1,3-dialkylpyrroles from inexpensive pyrrolidine and aldehydes.

Keywords: pyrrole, pyrrolidine, aldehyde, enamine, hydride shift

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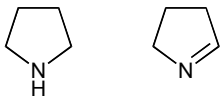
Various substituted pyrroles can be synthesized from pyrrole or simply substituted pyrroles by derivatization according to its inherent reactivity,[1,2] e.g., *N*-substitutions under basic conditions, normal electrophilic substitutions with suitable electrophiles at the α-carbon atom, and triisopropylsilyl(TIPS)-directed electrophilic substitutions at the β-carbon atom.[3] Otherwise, organic chemists must assemble a four-carbon unit in a heterocyclic skeleton to obtain desired pyrrole molecules,[4] as observed in Paar-Knorr and Knorr syntheses.[5] Although pyrrole derivatives have been widely used as pharmaceuticals and functional materials, preparations of pyrroles from primary starting materials such as commercially available inexpensive pyrrolidine (**1**) and easily accessible 1-pyrroline (**2**) are quite limited.[6] The difficulty can be ascribed mainly to inability of **1** to be oxidized and easy dimerization of **2**.[7] Here we present a facile non-oxidative method of synthesizing 1,3-disubstituted pyrroles from **1** and various aldehydes.

Chart 1

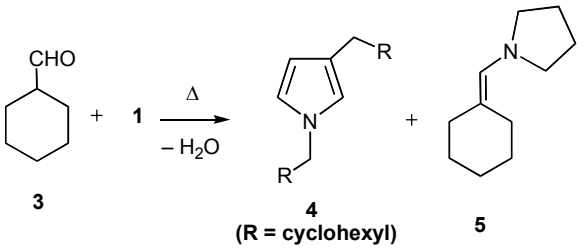


1 **2**

On heating a mixture of **1** and an excess of cyclohexanecarbaldehyde (**3**) in toluene using a

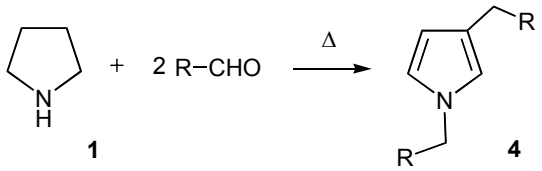
Dean-Stark apparatus,[8] under typical conditions of enamine synthesis, 1,3-bis(cyclohexylmethyl)pyrrole (**4**) was obtained in 17% yield, accompanied with enamine **5** (Scheme 1). The yield of **4** was improved up to 32% when a mixture of **3** and **5** was refluxed in toluene for 19 h and the addition of a catalytic amount of a Brønsted acid, such as *p*- toluenesul fonic acid, pyridinium *p*-toluenesulfonate and sulfuric acid, was ineffective under the conditions.

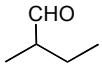
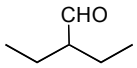
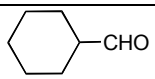
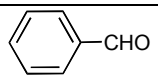
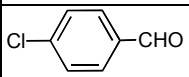
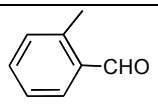
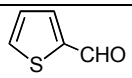
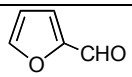
Scheme 1



Our attention was then directed towards pressurized reaction conditions because the reaction is basically to assemble three components, two aldehydes and one pyrrolidine. Under pressurized conditions, various aldehydes were transformed into the corresponding 1,3-disubstituted pyrroles.[9] Results are shown in Table 1. Among the solvents used in the reaction of isobutyraldehyde (entry 2–8), toluene gave slightly better yields than the other solvents used. Without any solvent the product was obtained in moderate yield (entry 1). Various benzaldehydes (entries 14–16) gave moderate yields of dibenzylpyrroles, whereas furan- and thiophenecarbaldehydes provided only low yields of the corresponding products (entries 17 and 18). The yields of 1,3-dioctyl- and 1,3-dihexylpyrroles from octanal and haxanal were low (entries 19 and 20). The reaction procedure is very simple. A solution of aldehyde and pyrrolidine in a solvent or without a solvent was charged in an autoclave and heated at 140–200 °C for an appropriate reaction time. The inner pressure was in the range of 0.5–2.0 MPa depending on the aldehyde and solvent used. After being cooled to room temperature, the reaction mixture was filtrated to remove solids formed and the solvent and water formed were removed with an evaporator. The residue was distilled or chromatographed to give the product.

Table 1. Results of reactions of pyrrolidine with various aldehydes under pressure



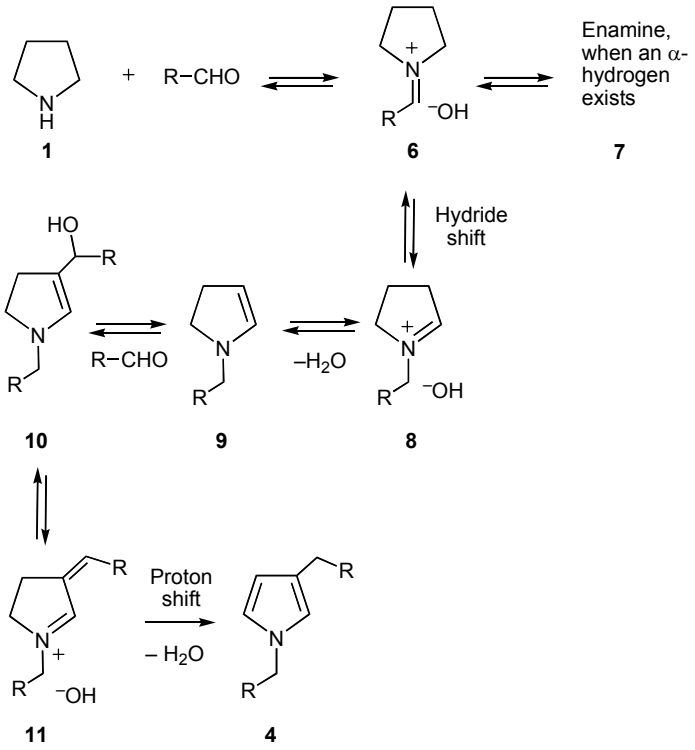
Entry	Aldehyde	Reaction conditions	Yield (%)[a]
1		No solvent, 180 °C, 24 h	58
2		EtOH,[b] 180 °C, 24 h	51
3		hexane,[b] 180 °C, 20 h	58
4		dioxane,[b] 160 ˚C, 60 h	61
5		toluene,[b] 200 °C, 12 h	66
6		toluene,[b] 180 °C, 20 h	79
7		toluene,[b] 160 °C, 60 h	76
8		toluene,[b] 140 °C, 72 h	71
9		toluene,[b] 200 °C, 12 h	62[c]
10		toluene,[b] 180 °C, 20 h	74[c]
11		toluene,[b] 200 °C, 12 h	65
12		toluene,[b] 180 °C, 21 h	76
13		toluene,[b] 180 °C, 20 h	79[c]
14		toluene,[b] 200 °C, 20 h	47
15		toluene,[b] 200 °C, 24 h	60
16		toluene,[b] 200 °C, 24 h	53
17		toluene,[b] 200 °C, 24 h	11
18		toluene,[b] 180 °C, 20 h	5
19	*n*-C_5H_{11}CHO	toluene,[b] 180 °C, 20 h	15
20	*n*-C_7H_{15}CHO	toluene,[b] 180 °C, 20 h	13

[a] Isolated yield after distillation [b] For 50 mmol of pyrrolidine, 100 ml of solvent

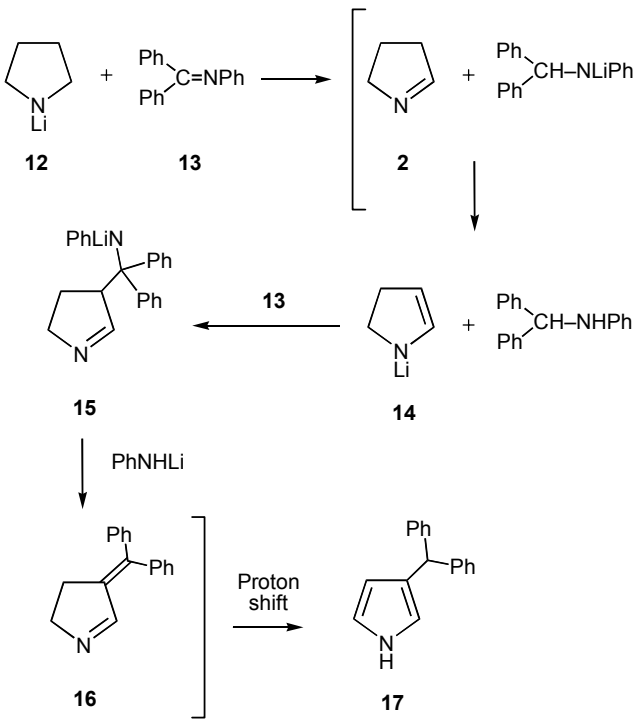
was used. [c] A mixture of the diastereomers was obtained.

The proposed reaction mechanism is illustrated in Scheme 2. The mechanism involves enamine **9**[10] as a key intermediate, which can be formed via a hydride shift from **6** to **8** in either intramolecular or intermolecular fashion and subsequent deprotonation. Enamine **9** captures another aldehyde to introduce a substituent at the 3 position of the pyrroline, followed by proton shift leading to **4**. Enamine **7** can be formed when at least one hydrogen exists at the α position of the aldehyde. However, enamines **7** derived from α-branched aldehydes have two alkyl substituents at the reacting olefinic carbon site and should show reduced reactivity toward aldehyde due to a steric hindrace.[11] In fact, reactions with α-branched aldehydes provided better yields of products than others, while those with *n*-alkanals gave low yields of products (entries 17 and 18). Gaining an aromatic ring in final products may be a driving force for this one-pot multi-stepped and multi-component reaction. The resemblance to a hydride shift and the reaction of the similar enamine intermediate with the aldehyde was proposed in the formation of 3,5-dibenzylpyridine from piperidine and benzaldehyde,[12] although the yield of pyridine was found to be less than 50%. In addition, Cook *et al*. proposed the formal 1,3-hydride shift in a conversion process between 3-pyrroline and ketones to *N*-substituted pyrroles.[13] In the literature we found only one similar reaction that yields 3-substituted pyrroles from **1** with imines under basic conditions;[14] Wittig et al. reported that lithium pyrrolidine amide (**12**) reacted with benzophenone imine (**13**) to give 3-(diphenylmethyl)pyrrole (**17**) in 35% yield. The proposed reaction mechanism requires the oxidation of the amide by the imine **13** to produce 1-pyrroline (**2**), which is deprotonated and then reacts with another **13** to give **17** via **15** and **16** (Scheme 3). Our method is clearly superior to Wittig's method due to the facility of our procedure and the substrates used, and, of course, the yields provided.

Scheme 2. A possible reaction mechanism for the synthesis of **4** from **1**



Scheme 3. The proposed reaction mechanism for the Wittig's reaction



In summary, we have found a facile non-oxidative method for synthesizing 1,3-disubstituted pyrroles from pyrrolidine and aldehyde. α-Branched aldehydes and benzaldehyde provided

moderate to good yields of the products, although heterocyclic carbaldehydes and aldehydes with primary α carbon atom gave low yields of the products. The use of pyrrolidine is one of the advantages of this new method and the facility of the method increases the availability of these pyrroles as starting materials for functionalized materials. Mechanistic study and applications of this method for synthesizing biologically active and functionalized pyrroles are now in progress.

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9. All new compounds were characterized by spectroscopic and/or combustion analyses. Their selected data are as follows. **4** (R= 2-propyl): Colorless oil, bp = 65-68 ˚C/ 0.1 mmHg. ^{1}H NMR ($CDCl_3$) δ= 0.87 (d, J = 6.8 Hz, 6H), 0.89 (d, J = 6.8 Hz, 6H), 1.74 (nonet, J = 6.8 Hz, 1H), 1.98 (nonet, J = 6.8 Hz, 1H), 2.30 (d, J = 6.8 Hz, 2H), 3.57 (d, J = 6.8 Hz, 2H), 5.92 (dd, J = 2.4, 1.7 Hz, 1H), 6.36 (dd, J = 2.1, 1.7 Hz, 1H), 6.50 (dd, J = 2.4, 2.1 Hz, 1H) ppm; ^{13}C NMR ($CDCl_3$) δ= 20.0, 22.5, 29.9, 30.6, 36.6, 57.3, 108.3, 119.1, 120.4, 122.8 ppm; IR (liq. film) ν_{max} = 2954s, 2925m, 2904m, 2869m, 2844w, 2358w, 2343w, 1498m, 1467m, 1386w, 1365w, 1354w, 1324w, 1278w, 1162m, 1066w, 767m, 750w, 705w, 684w, 667w, 649w cm^{-1};MS (70 eV) m/z (rel int) 179 (M^+, 23), 137 (12), 136 (100), 80 (26); UV

(methanol) λ_{max} = 222sh (logε = 3.74) nm; HRMS Found: 179.1660. Calcd for $C_{12}H_{21}N$: M, 179.1674. **4** (R=2-butyl, a mixture of diastereomers): ^{1}H NMR ($CDCl_3$) δ = 0.83 (d, J = 6.6 Hz, 3H), 0.86 (d, J = 6.6 Hz, 3H), 0.89 (t, J = 7.4 Hz, 3H), 0.90 (t, J =7.4 Hz, 3H), 1.05-1.17 (m, 2H), 1.31-1.43 (m, 2H), 1.50-1.54 (m, 1H), 1.73-1.79 (m, 1H), 2.23 (dd, J = 14.1, 7.7 Hz, 1H), 2.43 (dd, J = 14.1, 5.9 Hz, 1H), 3.54 (dd, J = 13.7, 7.6 Hz, 1H), 3.70 (dd, J = 13.7, 6.7 Hz, 1H), 5.92 (dd, J = 2.4, 1.7 Hz, 1H), 6.36 (dd, J = 2.1, 1.7 Hz, 1H), 6.50 (dd, J = 2.4, 2.1 Hz, 1H) ppm. **4** (R=3-pentyl): ^{1}H NMR ($CDCl_3$) δ = 0.87 (t, J = 7.6 Hz, 12H) 1.22-1.37 (m, 8H), 1.37 (septet, J = 6.4 Hz, 1H), 1.61 (septet, J = 6.4 Hz, 1H), 2.37 (d, J = 6.4 Hz, 2H), 3.68 (d, J = 6.4 Hz, 2H), 5.92 (dd, J = 2.4, 1.7 Hz, 1H), 6.36 (dd, J = 2.1, 1.7 Hz, 1H), 6.50 (dd, J = 2.4, 2.1 Hz, 1H) ppm; ^{13}C NMR ($CDCl_3$) δ = 10.6, 11.0, 23.3, 25.1, 30.4, 42.2, 42.7, 52.7, 108.3, 119.2, 120.4, 122.4 ppm. **4** (R=cyclohexyl): ^{1}H NMR ($CDCl_3$) δ = 0.85-0.94 (m, 4H) 1.08-1.26 (m, 6H), 1.39 (ttt, J = 11.2, 6.8, 3.4 Hz, 1H), 1.58-1.75 (m, 11H), 2.30 (d, J = 6.8 Hz, 2H), 3.59 (d, J = 7.1 Hz, 2H), 5.91 (dd, J = 2.4, 1.7 Hz, 1H), 6.34 (dd, J = 2.1, 1.7 Hz, 1H), 6.49 (dd, J = 2.4, 2.1 Hz, 1H) ppm; ^{13}C NMR ($CDCl_3$) δ = 25.7, 26.3, 26.4, 26.7, 30.8, 33.3, 35.2, 39.5, 39.8, 56.1, 108.2, 119.1, 120.4, 122.3 ppm. **4** (R=1-phenethyl, a mixture of diastereomers): ^{1}H NMR ($CDCl_3$) δ = 1.17 (d, J = 7.2 Hz, 3H), 1.21 (d, J = 6.8 Hz, 3H), 2.58 (m, 1H), 2.74 (m, 1H), 2.86 (m, 1H), 3.04 (m, 1H), 3.78 (dd, J = 13.6, 7.8 Hz, 1H), 3.91 (dd, J = 13.6, 6.8 Hz, 1H), 5.82 (m, 1H), 6.16 (m, 1H), 6.36 (dd, J = 2.4, 2.2 Hz, 1H), 7.08-7.30 (m, 10H) ppm. **4** (R=phenyl): ^{1}H NMR ($CDCl_3$) δ = 3.81 (s, 2H), 4.94 (s, 2H), 6.00 (dd, J = 2.4, 1.7 Hz, 1H), 6.41(dd, J = 2.1, 1.7 Hz, 1H), 6.58 (dd, J = 2.4, 2.1Hz, 1H), 7.07-7.34 (m, 10H) ppm; ^{13}C NMR ($CDCl_3$) δ = 33.5, 53.2, 109.0, 119.3, 121.2, 123.5, 125.6, 126.9, 127.5, 128.2, 128.6, 128.6, 138.2, 142.3 ppm. **4** (R=*p*-chlorophenyl): ^{1}H NMR ($CDCl_3$) δ = 3.76 (s, 2H), 4.93 (s, 2H), 5,98 (dd, J = 2.4, 1.7 Hz, 1H), 6.38 (dd, J = 2.1, 1.7, 1H), 6.57 (dd, J = 2.4, 2.1 Hz, 1H), 7.01 (dm, J = 8.3 Hz, 2H), 7.15 (dm, J = 8.3 Hz, 2H), 7.22 (dm, J = 8.3 Hz, 2H), 7.27 (dm, J = 8.3 Hz, 2H) ppm; ^{13}C NMR ($CDCl_3$) δ = 32.8, 52.6, 109.2, 119.1, 121.3, 123.4, 128.3, 128.3, 128.8, 129.9, 131.3, 133.4, 136.7, 140.7 ppm. **4** (R=*o*-tolyl): ^{1}H NMR ($CDCl_3$) δ = 2.24 (s, 3H), 2.29 (s, 3H), 3.79 (s, 2H), 4.96 (s, 2H), 5.97 (dd, J = 2.4, 1.7 Hz, 1H), 6.30-6.32 (m, 1H), 6.53 (dd, J = 2.4, 2.1 Hz, 1H), 6.82 (d, J = 7.2 Hz, 1H), 7.09-7.19 (m, 7H) ppm; ^{13}C NMR ($CDCl_3$) δ = 18.9, 19.4, 31.2, 51.3, 108.9, 119.4, 121.1, 122.6, 125.8, 125.9, 126.3, 127.7, 127.7, 129.2, 130.0, 130.2, 135.7, 136.2 ppm. **4** (R=2-thienyl): ^{1}H NMR ($CDCl_3$) δ = 3.99 (s, 2H), 5.12 (s, 2H), 6.06 (dd, J = 2.4, 1.7 Hz, 1H), 6.55 (dd, J = 2.1, 1.7 1H), 6.63 (dd, J = 2.4, 2.1 Hz, 1H), 6.80-6.81 (m, 1H), 6.88-6.94 (m, 3H), 7.08-7.10 (m, 1H), 7.20-7.22 (m, 1H) ppm. ^{13}C NMR ($CDCl_3$) δ = 27.7, 48.0, 109.1, 118.8, 120.8, 123.1, 123.2, 124.2, 125.5, 125.9, 126.6, 126.9, 140.6, 145.8 ppm. **4** (R=furyl): ^{1}H NMR ($CDCl_3$) δ = 3.80 (s, 2H), 4.94 (s, 2H), 5.99 (dd, J = 3.2, 0.6 Hz, 1H), 6.05 (dd, J = 2.4, 1.7 Hz, 1H), 6.23 (dd, J = 3.2, 0.6 Hz, 1H), 6.27 (dd, J = 3.2, 1.6 Hz, 1H), 6.31 (dd, J = 3.2, 1.6 Hz, 1H), 6.54 (dd, J = 2.1, 1.7 Hz, 1H), 6.61 (dd, J

= 2.4, 2.1 Hz, 1H), 7.30 (dd, *J* = 1.8, 0.6 Hz, 1H), 7.36 (dd, *J* = 1.8, 0.6 Hz, 1H) ppm; ^{13}C NMR ($CDCl_3$) δ = 26.1, 46.0, 105.1, 108.1, 109.0, 110.1, 110.4, 118.8, 120.2, 120.7, 140.9, 142.6, 150.7, 155.8 ppm. **4** (R=1-pentyl): ^{1}H NMR ($CDCl_3$) δ = 0.86-0.90 (m, 6H), 1.28-1.30 (m, 12H), 1.51-1.59 (m, 2H), 1.68-1.76 (m, 2H), 2.44 (t, *J* = 7.8 Hz, 2H), 3.77 (t, *J* = 7.4 Hz, 2H), 5.95 (dd, *J* = 2.4, 1.7 Hz, 1H), 6.40 (dd, *J* = 2.1, 1.7 Hz, 1H), 6.52 (dd, *J* = 2.4, 2.1 Hz, 1H) ppm; ^{13}C NMR ($CDCl_3$) δ = 14.0, 14.1, 22.5, 22.7, 26.5, 27.1, 29.2, 31.3, 31.4, 31.5, 31.8, 49.5, 107.7, 117.7, 120.0, 124.4 ppm. **4** (R=1-heptyl): ^{1}H NMR ($CDCl_3$) δ = 0.87 (t, *J* = 6.8 Hz, 6H), 1.25-1.28 (m, 22H), 1.73 (m, 2H), 2.43 (t, *J* = 7.8 Hz, 2H), 3.78 (t, *J* = 7.2 Hz, 2H), 5.96 (dd, *J* = 2.4, 1.7 Hz, 1H), 6.41 (dd, *J* = 2.1, 1.7 Hz, 1H), 6.54 (dd, *J* = 2.4, 2.1 Hz, 1H) ppm; ^{13}C NMR ($CDCl_3$) δ = 14.1, 14.1, 22.6, 22.7, 26.8, 27.1, 29.2, 29.2, 29.3, 29.5, 29.6, 31.3, 31.6, 31.8, 31.9, 49.5, 107.7, 117.7, 120.1, 124.5 ppm.

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