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Stereoselective Synthesis of 3-Carboxy-4,5-dihydropyrroles via an Intramolecular Iminium Ion Cyclization Reaction

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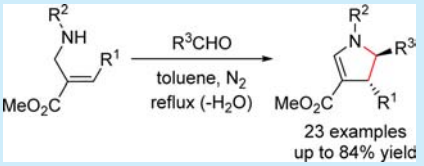
Supporting Information

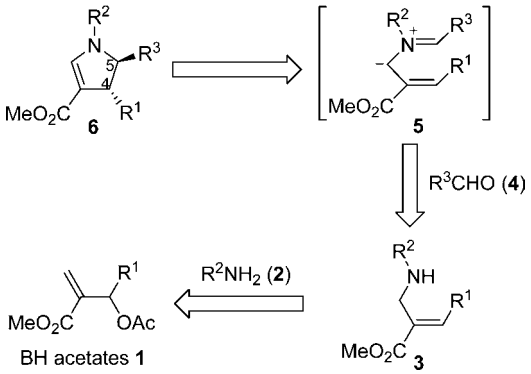
ABSTRACT: An efficient and practical method has been developed for the synthesis of *trans*-4,5-disubstituted 3-carboxy-4,5-dihydropyrroles via an intramolecular iminium ion cyclization reaction of readily accessible Baylis–Hillman derivatives and aldehydes in moderate to high yield. These new dihydropyrroles could be easily converted to pyrroles or pyrrolidines.



The dihydropyrrole framework is a valuable structural motif found in a number of natural products and pharmaceutical agents.[1] 3-Carboxy-4,5-dihydropyrroles were not only shown to possess interesting biological activities[2] but also used as key intermediates in the synthesis of natural products[3] and bioactive agents.[4] Consequently, synthesis of 3-carboxy-dihydropyrroles has drawn attention from both organic and medicinal chemists.[5−11] The commonly used methods include applications of the [3 + 2] cycloaddition,[6] reaction of acyclic imides with 1-(ethoxycarbonyl)cyclopropyltriphenylphosphonium tetrafluoroborate,[7] nucleophilic amine ring-opening cyclization of donor−acceptor cyclopropanes,[8] iodocyclization of alkenyl-substituted β-enamino esters,[9] and Ce(IV)-mediated oxidative addition of allyltrimethylsilane to β-carbonyl imines.[10] Recently, continuing efforts in this area have led to several new synthetic approaches.[11] For example, Ma's group disclosed a versatile palladium-catalyzed domino three-component reaction of 2-(2,3-allenyl)acylacetates with organic halides and amines;[11a] Wang's group reported the $BF_3{\cdot}Et_2O$-promoted three-component reaction of propargylic alcohols with 2-butynedioates and benzyl-*i*-propylamine;[11b] Zhang's group described the DBU-catalyzed [3 + 2] cycloaddition of electron-deficient 1,3-conjugated enynes with 2-aminomalonates;[11c] France's group reported $Ni(ClO_4)_2{\cdot}6H_2O$-catalyzed nucleophilic amine ring-opening cyclization of donor−acceptor cyclopropanes under milder reaction conditions.[11d] Despite the numerous methods reported to date, there are few that are efficient for the synthesis of 3-carboxy-4,5-dihydropyrroles with a controlled 4,5-substitution pattern.[5d,11a,c]

Baylis−Hillman adducts and their derivatives have been proven to be efficient starting materials for the synthesis of useful carbo- and heterocycles.[12] As part of our continuing interest in the utilization of iminium ions in the synthesis of heterocycles,[13] we envisioned that 3-carboxy-4,5-dihydropyrrole **6** could be readily prepared from key precursor **3**, prepared from simple Baylis−Hillman acetate **1** and a primary amine (Scheme 1). The reaction of **3** and an aldehyde could form iminium ion intermediate **5** which may undergo a cyclization reaction *in situ* to result in the target dihydropyrrole. Herein, the details of these studies are presented.

Scheme 1. Synthetic Strategy to 4,5-Dihydropyrrole 6



As expected, the key precursors **3** were readily prepared from the known Baylis−Hillman acetates **1**[14] and primary amines **2** in good to excellent yields (Table 1).[15] The stereochemistry of these amines was determined as the *E*-configuration based on the vinylic proton at 7.74−7.96 ppm (singlet) in ^{1}H NMR spectra.[15a] As shown in Table 1, R^1 is aryl and R^2 can be aliphatic or aromatic.

Treatment of acrylate **3a** with 1.2 equiv of benzaldehyde for 0.5 h in refluxing toluene with water removal via a Dean−Stark trap gave the desired product **6a** in 79% yield (entry 1, Table 2).[16] Both an LC−MS and ^{1}H NMR spectrum of the crude product indicated that **6a** is a single isomer. The *trans* configuration was based on the coupling pattern at 4.16 and 4.32 ppm ($J_{4,5}$ = 7.2 Hz) of ^{1}H NMR.[17] The reaction results of precursors **3** (shown in Table 1) and various aldehydes are summarized in Table 2. In general, the desired 3-carboxy-dihydropyrroles **6** were obtained in good to high yields with various functional groups (e.g., nitro, cyano, halo, and methoxy) at the benzene ring of R^1 and R^3. The *trans*

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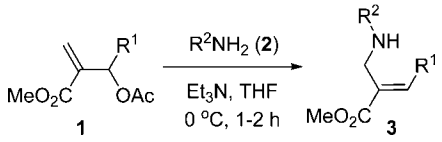
Table 1. Synthesis of Key Precursors 3[a]



entry	R^1	R^2	3	yield (%)[b]
1[c]	Ph	Me	**3a**	90
2	Ph	*n*-Bu	**3b**	79
3	Ph	*i*-Pr	**3c**	67
4	Ph	Bn	**3d**	78
5[d]	Ph	Ph	**3e**	61
6	4-NO_2Ph	*n*-Bu	**3f**	67
7	4-CNPh	*n*-Bu	**3g**	60
8	4-ClPh	*n*-Bu	**3h**	73
9	4-MePh	*n*-Bu	**3i**	82
10	2-MePh	*n*-Bu	**3j**	73
11	4-MeOPh	*n*-Bu	**3k**	69
12	2-MeOPh	*n*-Bu	**3l**	64

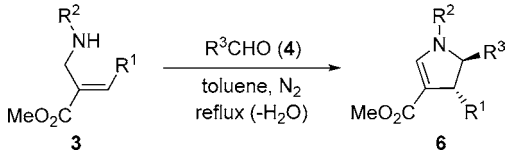
[a]Reagents and conditions (except where designated): **1** (1.0 equiv), **2** (2.0 equiv), and Et_3N (1.0 equiv) in THF, 0 °C. [b]Isolated yield. [c]Methylamine alcohol solution (30%) was used. [d]**1a** (1.0 equiv) and aniline (1.5 equiv) in H_2O, 80 °C, 5 h.

selectivity observed for compound **6a** held true for all the desired products, which were determined by comparison of ^{1}H NMR spectra with that of compound **6a**.

As disclosed in Table 2, aromatic aldehydes participated in the current reaction effectively to produce the desired products in moderate to high yields (entries 1−12, Table 2). Both electron-rich and -deficient aldehydes gave good yields, suggesting that the current reaction is less sensitive to electronic factors on the aromatic aldehydes. In contrast, enolizable aliphatic aldehydes failed in the current reaction (entry 13, Table 2),[16,18] which could prevent the formation of the reactive iminium ion intermediate. Pivalaldehyde also failed to give any desired product which might be too hindered for the cyclization (entry 14, Table 2). On the other hand, cyclohexanecarbaldehyde was a good substrate for the current reaction, producing the desired product **6o** in 56% yield (entry 15, Table 2). When R^2 = *n*-Bu and R^3 = Ph, various R^1 groups are compatible for the current reactions to yield the expected products **6** (entries 16−23, Table 2). Aliphatic groups were suitable as R^2 for the current cyclization reaction (entries 1, 16, 24, 25, Table 2). When R^2 = *i*-Pr, a 50% yield of **6x** and 31% yield of *cis*-isomer **8x** ($J_{4,5}$ = 18.9 Hz) were obtained (entry 24, Table 2). This result is consistent with the reaction mechanism (see later section). However, when R^2 = Ph, only a trace amount with the molecular ion corresponding to product **6z** was detected by LC-MS after 36 h (entry 26, Table 2). This was very likely due to the difficulty in forming the iminium ion between a secondary aromatic amine and an aldehyde. Moreover, we also attempted to expand the scope of this reaction to ketones (e.g., cyclohexanone, acetophenone); the reactions failed to afford the desired 3-carboxy-dihydropyrroles.

A plausible mechanism for the formation of products **6** and **8** is outlined in Scheme 2. It was proposed that the cyclization reaction proceeded through an azomethine ylide formed from the condensation of compound **3** with an aldehyde. When R^2 = Me, *n*-Bu, or Bn, the thermal 6π electrocyclization of favored azomethine ylide **5** with a disrotatory mode gives the expected *trans*-configuration products **6**.[19] When R^2 = *i*-Pr, intermediate

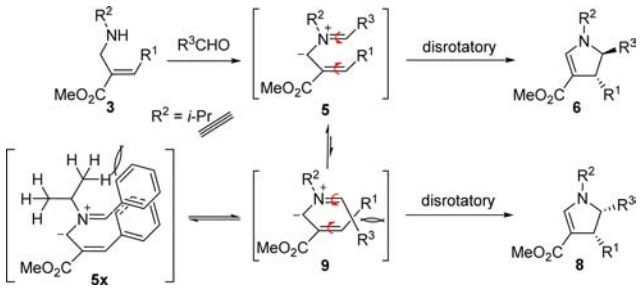
Table 2. Synthesis of 4,5-Dihydropyrroles 6[a,b]



entry	R^1	R^2	R^3	time (h)	6	yield (%)[c]
1	Ph	Me	Ph	0.5	**6a**	79
2	Ph	Me	4-NO_2Ph	3	**6b**	62
3	Ph	Me	4-CNPh	1.5	**6c**	68
4	Ph	Me	4-ClPh	4	**6d**	53
5	Ph	Me	3-ClPh	0.5	**6e**	67
6	Ph	Me	2-ClPh	0.5	**6f**	72
7	Ph	Me	4-MePh	1.5	**6g**	78
8	Ph	Me	3-MePh	1	**6h**	77
9	Ph	Me	2-MePh	0.5	**6i**	75
10	Ph	Me	4-MeOPh	3	**6j**	78
11	Ph	Me	2-MeOPh	3.5	**6k**	67
12	Ph	Me	2-thienyl	1	**6l**	73
13[d]	Ph	Me	*n*-Pr	4	**6m**	0
14[e]	Ph	Me	*t*-Bu	4	**6n**	0
15	Ph	Me	*c*-Hex	1	**6o**	56
16	Ph	*n*-Bu	Ph	1	**6p**	75
17	4-NO_2Ph	*n*-Bu	Ph	1.5	**6q**	66
18	4-CNPh	*n*-Bu	Ph	1.5	**6r**	73
19	4-ClPh	*n*-Bu	Ph	1.5	**6s**	79
20	4-MePh	*n*-Bu	Ph	1.5	**6t**	84
21	2-MePh	*n*-Bu	Ph	1.5	**6u**	75
22	4-MeOPh	*n*-Bu	Ph	1.5	**6v**	77
23	2-MeOPh	*n*-Bu	Ph	1	**6w**	66
24	Ph	*i*-Pr	Ph	6	**6x**	50[f]
25	Ph	Bn	Ph	2	**6y**	79
26[g]	Ph	Ph	Ph	36	**6z**	trace

[a]All reactions were performed on 0.5 mmol scale using 1.2 equiv of aldehydes in refluxing toluene with a Dean−Stark trap under nitrogen. [b]Cis isomer was not obtained except for substrate **3c** (entry 24). [c]Isolated yield. [d]35% of starting material **3a** was recovered, and 20% yield of byproduct (2*E*,2′*E*)-dimethyl 2,2′-(methylazanediyl)bis-(methylene)bis(3-phenylacrylate) **7a** was isolated. [e]32% of starting material **3a** was recovered, and 26% yield of byproduct **7a** was isolated. [f]The trans/cis ratio is 62:38, and 31% of cis-isomer **8x** was isolated. [g]Trace amount with molecular ion corresponding to desired product **6z** was detected by LC-MS.

Scheme 2. Proposed Reaction Mechanism



5 undergoes isomerization to intermediate **9** due to the repulsion between the methyl of *i*-Pr and the phenyl of azomethine ylide; the competition of transition states **5x** and **9x** leads to a mixture of isomers **6x** and **8x**.

The new dihydropyrrole product **6a** could be readily transformed to pyrrole **10a** with DDQ oxidation in CH_2Cl_2

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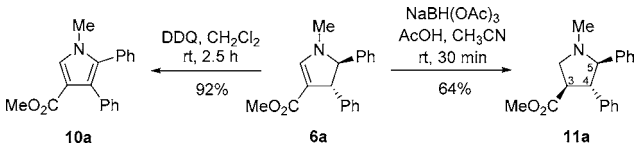
at room temperature (Scheme 3).[20] In addition, reduction of **6a** using $NaBH(OAc)_3$ gave 3,4,5-trisubstituted pyrrolidine **11a**

Scheme 3. Synthetic Derivatization of Dihydropyrroles



with the configuration as indicated (Scheme 3).[21] The *trans*–*trans* configuration was based on the coupling pattern at 3.19 and 3.58 ppm ($J_{3,4}$ = 7.5 Hz) and the coupling pattern at 3.58 and 3.67 ppm ($J_{4,5}$ = 8.4 Hz) of ^{1}H NMR.[17a] Thus, highly substituted pyrroles and pyrrolidines are readily accessible using the method.

In summary, we have developed an efficient and practical strategy for the synthesis of *trans*-4,5-disubstituted 3-carboxy-4,5-dihydropyrroles via an intramolecular iminium ion cyclization reaction of Baylis–Hillman derivatives with aldehydes in moderate to high yield. The synthetic utility of the dihydropyrroles obtained via this new method was further demonstrated by oxidation to the corresponding pyrroles or reduction to pyrrolidines with multiple substituents and a *trans*–*trans* configuration. This new method to access dihydropyrroles compliments the existing collection of methods, which should allow rapid synthesis of compounds containing the dihydropyrrole moiety.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.5b01787.

Experimental procedures, full characterization data, copies of LC-MS-ELSD and NMR spectra for all products (PDF)

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Notes

The authors declare no competing financial interest.

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