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Novel Synthetic Methods for Disubstituted Pyrroles from Pyrrolidine and 2-Substituted 1-Pyrrolines

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ABSTRACT

Development of facile synthetic methods for various disubstituted pyrroles from pyrrolidine and 2-substituted 1-pyrrolines is reviewed based on our recent findings. Various 1,3-disubstituted pyrroles were synthesized by reaction of pyrrolidine and aldehyde heating without any catalyst. On the other hand, 2,3-disubstituted pyrroles were synthesized from 2-substituted 1-pyrrolines by a sequece involving its aldol-type condensation with aldehyde and subsequent base-catalyzed double-bond isomerization. Application of the former method to one-pot synthesis of a pyrrolocyclophane and preparation of N-substituted indoles from indoline and aldehydes is disclosed. Some pyrrole products by the latter method were transformed into dipyrrin derivatives via their pyrrole-2-carbaldehydes, and chemical and structural properties of the dipyrrin derivatives are described.

Keywords: Pyrroles, Pyrrolidine, 1-Pyrrolines, Pyrrolophanes, Indoles, Dipyrrins

I. INTRODUCTION

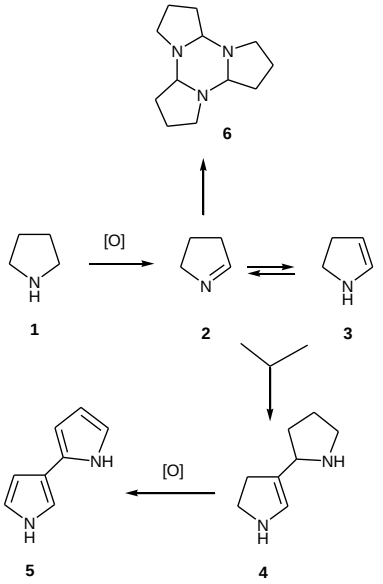
Pyrrole derivatives are an important class of nitrogen-containing heterocyclic compounds especially because of their significance in the synthesis of natural products, pharmaceuticals and functionalized materials.[1] Although there are many classical synthetic methods, such as Knorr,[2] Paal–Knorr,[3] Hantzsch[4], and Barton-Zard[5] syntheses, synthetic methodologies for pyrroles have been continuously developed.[6] Particularly, the development of nitrogen-containing five-membered rings by transition-metal catalyzed reactions is a recent topic of interest.[7] Besides, synthetic routes for pyrroles by inexpensive or easily available hydrogenated materials such as pyrrolines and pyrrolidines are also still important. In this review, we describe development of two facile synthetic methods for 1,3-disubstituted pyrroles from commercially available inexpensive pyrrolidine and 2,3-disubstituted pyrroles from easily accessible 2-substituted 1-pyrrolines, based on our fingings.

II. METHODS AND MATERIAL

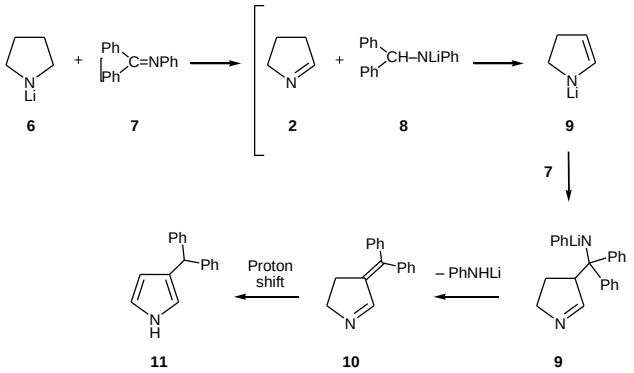
1. 1,3-Disubstituted Pyrroles Form Pyrrolidine

Direct dehydrogenation of pyrrolidine (**1**) and 1-pyrroline (**2**) to pyrrole has been often hampered by formation of by-products.[8] The difficulty can be ascribed mainly to instability of **2**, which is tautomerized with 2-pyrroline (**3**). Compound **2** generated easily reacts with the isomer **3** to give **4** and **5**, or cyclizes to trimer **6** (Scheme 1).[9-10] Although the formation of **4** from **3** indicates direct activation of *β*-C–H of pyrrolidine, a synthetic method involving such activation has not been developed. In 1971 Wittig *et al*. reported the synthesis for 3-substituted pyrroles from pyrrolidine under strong basic conditions as shown in Scheme 2.[11] Although the yields of the pyrroles by this method are less than 40%, this reaction should be recognized as the first example of activation of *β*-C–H bond of pyrrolidine. While activation of *α*-C–H bond of pyrrolidine has been extensively studied for a long

time,[12] pyrrole synthesis from pyrrolidine with activation of β-C–H bond was scarcely examined. In 2007, we unexpectedly found that pyrrolidine (**1**) reacts with two molecules of various aldehydes to give 1,3-disubstituted pyrroles.[13]



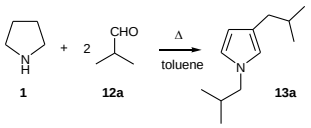
Scheme 1. The fate of pyrrolidine (**1**) under oxidative conditions.



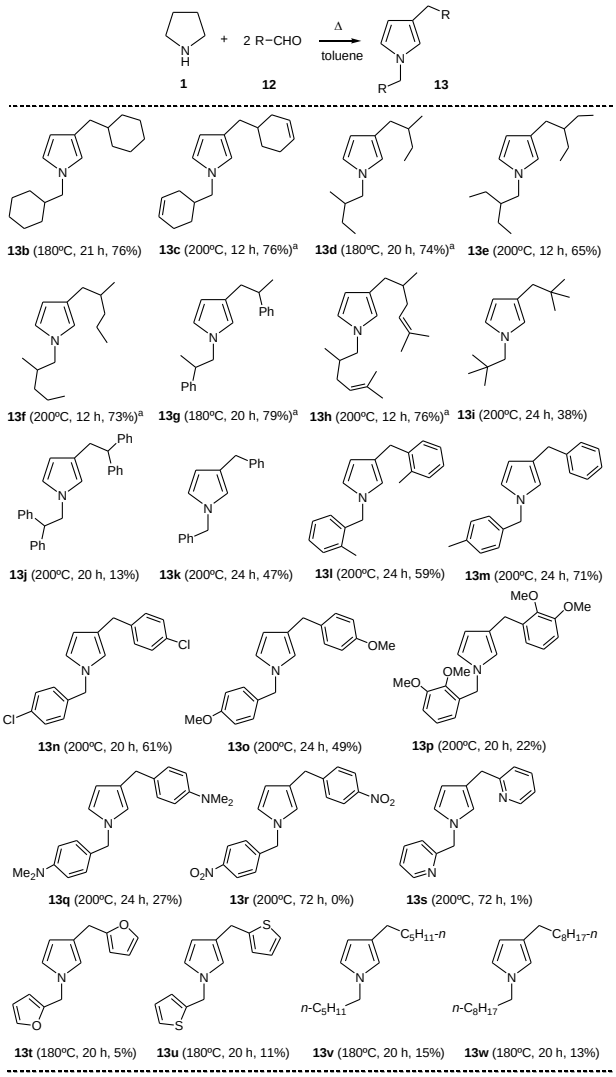
Scheme 2. The Wittig's method for synthesizing 3-substituted pyrrole from pyrrolidine.

Table 1 shows results of the reaction of **1** with isobutyraldehyde (**12a**) under various conditions. Among the solvents used in the reaction with **12a**, reactions in toluene gave slightly better yields than those in the other solvents. Without solvent the product was obtained in 58% yield (entry 1). Under the pressurized conditions, various aldehydes were found to react with pyrrolidine to produce the corresponding 1,3-disubstituted pyrroles. Scheme 3 shows substrate scope of this pyrrole synthesis. Some α-branched aldehydes react to give 1,3-disubstituted pyrroles **13b**–**13h** in good yields. The reactions with various benzaldehydes resulted in moderate yields of 1,3-dibenzylpyrroles **13k**–**13o**, whereas the reaction of electron-deficient 4-nitrobenzaldehyde **13r** resulted in no desired product. Those with 2,3-dimethoxy and 4-dimethylaminobenzaldehydes provided low yields of the products **13p–13q**. The reactions with heterocyclic carbaldehydes produced only a trace amount of the products **13s–13u**. The yields of 1,3- dioctyl- and 1,3-dihexyl-pyrroles in the reactions with octanal and haxanal were found to be also low. The reaction procedure is very simple. A solution of aldehyde and pyrrolidine (in a ratio of 2 to 1) in a solvent was charged in an autoclave and heated at 140–200 °C for an appropriate reaction time. The inner pressure was found to be in the range of 0.5–2.0 MPa depending on the aldehyde and the solvent used. After being cooled to room temperature, the reaction mixture was filtrated to remove a trace amount of black solids formed, and the solvent and water formed were removed with an evaporator. The residue was purified by distillation or chromatography to provide the product. Since the method is very facile, the procedure can be easily applied to a large-scaled synthesis.

Table 1. Results of reaction of pyrrolidine with **12a** under pressure

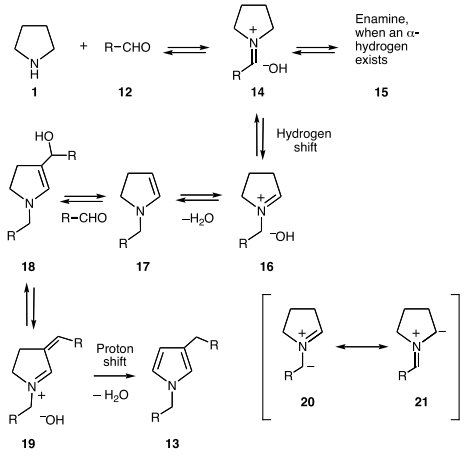


Entry	Reaction conditions	Isolated yield of **13a**
1	No solvent, 180 °C, 24 h	58%
2	EtOH, 180 °C, 24 h	51%
3	hexane, 180 °C, 20 h	58%
4	dioxane, 160 ˚C, 60 h	61%
5	toluene, 200 °C, 12 h	66%
6	toluene, 180 °C, 20 h	79%
7	toluene, 160 °C, 60 h	76%
8	toluene, 140 °C, 72 h	71%



[a]A mixture of the diastereomers was obtained.

Scheme 3. Scope of the pyrrole synthesis



Scheme 4. A possible reaction mechanism from **1** to **13**

The proposed reaction mechanism is illustrated in Scheme 4. Enamine **17** is a key intermediate, which can be formed via a hydrogen shift from **14** to **16**. For this shift, a proton transfer via methine ylide **20** (or **21**) is very plausible rather than a hydride transfer. Enamine **17** captures another aldehyde to introduce a substituent at the 3 position of the pyrroline, followed by proton shift leading to the final product **13** via **19**. Enamine **15** can also be formed when at least one hydrogen atom exists at the α position of the aldehyde, and it can react with another aldehyde. However, enamine **15** derived from α-branched aldehyde has two alkyl substituents at the reacting olefinic carbon atom and should show less reactivity toward aldehyde because of a steric reason. In fact, the reactions with α-branched aldehydes provided better yields of products than others, and the reactions with *n*-alkanals gave low yields of products **13v** and **13w**. Gaining an aromatic pyrrole ring in the final products may be a driving force for this one-pot multi-stepped and multi-component reaction. Recently it was found that the reaction time could be reduced by adding triethylamine without changing the yield, as shown in Figure 1. Although there is no evidence to account for how the amine works, it could help the proton shift from **14** to **16** via **20** (**21**).

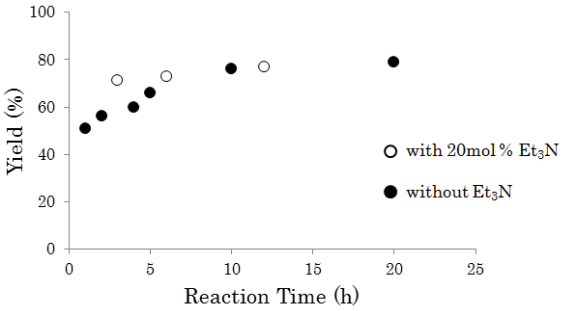
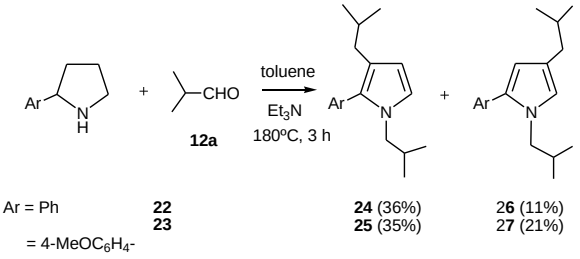
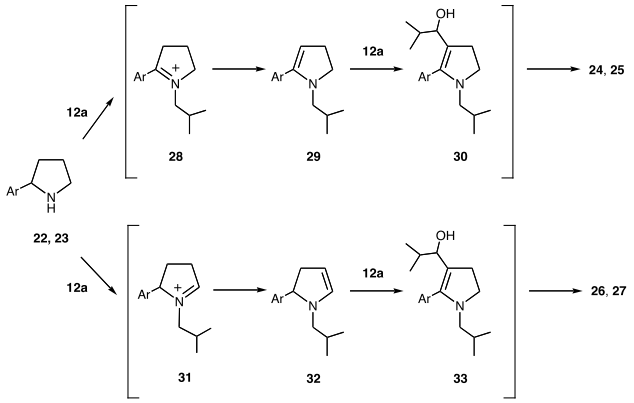


Figure 1. An effect of addition of triethylamine on the isolated yields of **13a**.

When 2-arylpyrrolidines were used instead of pyrrolidine in this pyrrole synthesis, 1,2,3- and 1,2,4-substituted pyrroles were obtained (Scheme 5).[14] The 1,2,3-substituted pyrroles, **24** and **25**, were obtained in better yield than those of 1,2,4-substituted pyrroles, **26** and **27**, respectively. The regioselectivity may be attributed to the stability of the iminium intermediate **28** over **31** by a resonance effect between the aryl group and the iminium moiety (Scheme 6).



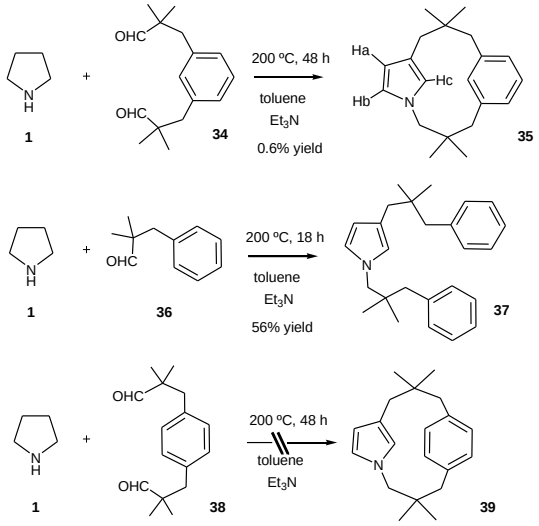
Scheme 5. Reactions of 2-arylpyrrolidines **22** and **23** with isobutyraldehyde.



Scheme 6. Possible reaction intermediates in the reaction of 2-arylpyrrolidines **22**–**23** with isobutyraldehyde.

2. Pyrrolophane Synthesis

In the previous section, development of synthesis of 1,3-substituted pyrroles from pyrrolidine and aldehyde is described. The reaction is a three-component assembling process and two substituents in the pyrrole product are derived from two molecules of aldehyde. Therefore, application of this reaction with a dialdehyde compound was envisioned to produce a corresponding cyclophane having a pyrrole, so called pyrrophane. According to this idea, some dialdehydes were subjected to the reaction with pyrrolidine under the pressurized conditions. The reaction of **1** and *m*-phenylene-bis(2,2-dimethylpropanal) **34** produced *m,m*-pyrrolophane **35** as expected. Howevere, its yield was found very poor compared with that of structurally related pyrrole **37** obtained by the reaction of **1** and **36** (Scheme 7).[15] Synthesis of *m,p*-pyrrolophane **39** was also attempted in a similar way with *p*-phenylene-bis(2,2-dimethylpropanal) **38**, but the desired cyclophane **39** was not obtained. The structure of **35** was confirmed by spectroscopic analysis.[16] Its conformation was deduced by ^{1}H NMR analysis. Clear up-field shifts of Ha and Hb in the pyrrole and the hydrogen atoms in the benzene



Scheme 7. Synthesis of pyrrolophane **35** and the related compound **37**.

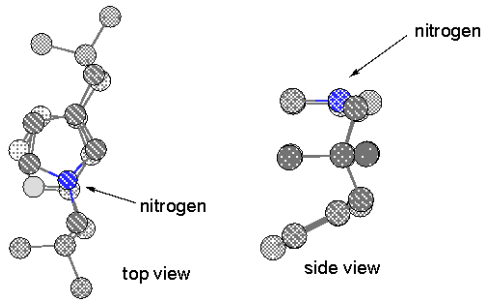
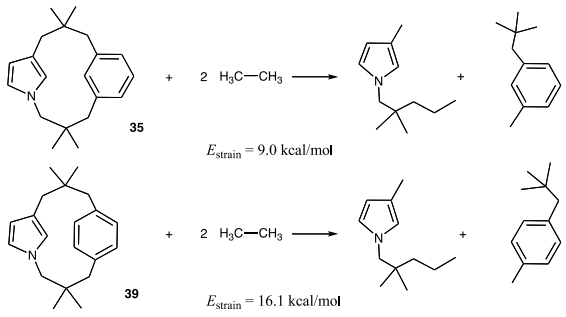


Figure 2. The most stable comformer for **35** calculated by B3LYP/6-31G(d) calculations. Hydrogen atoms are omitted for clarity.



Scheme 8. Hypothetical schemes for estimation of strain energies of pyrrolophanes **35** and **39**.

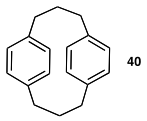


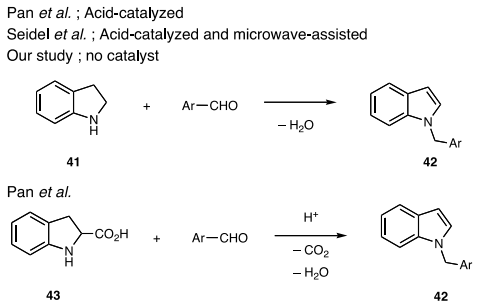
Figure 3. Structure of [3,3]paracyclophane **40**.

and no shift of Hc in the pyrrole of **35**, compared with chemical shift values of the corresponding hydrogen atoms of **37**, are observed. This can be explained best by the shielding effect of the aromatic rings when **35** exists as a conformer shown in Figure 2. Based on DFT calculations at B3LYP/6-31G(d) level of theory,[17] this conformer is expected to be the most stable one among eight possible conformers generated. According to Scheme 8, strain energies of **35** and **39** were evaluated by calculations at the same level of theory. A strain energy for *m,p*-cyclophane **39** is estimated to be 16.1 kcal/mol, which is slightly more than that (12.0 kcal/mol) estimated experimentally for [3,3]paracyclophane **40** (Figure 3),[18] and that (9.0 kcal/mol) for *m,m*-cyclophane **35** is relatively less than those. Probably, the large strain energy in **39** may make it difficult for **39** to form in the reaction.

III. RESULTS AND DISCUSSION

1. Substituted Indole Form Indoline

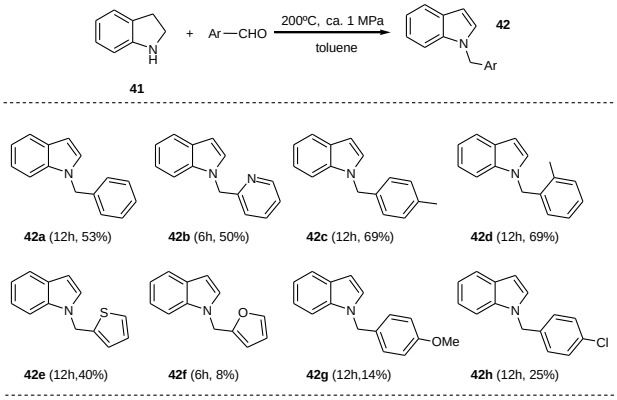
N-Alkylindoles are also important synthetic materials for biologically active natural products and drug candidates.[18–19] Although indoline can be oxidized into indole[20] and easily alkylated to afford *N*-alkylindoles,[21] there has scarcely been reported a one-step procedure directly from indoline to *N*-alkylindoles. Recently, Pan *et al.* reported the acid-catalyzed transformation of indoline (**41**) with arenecarbaldehydes into *N*-arylmethylindoles (**42**) (Scheme 9),[22] and Seidel *et al.* also reported the acid-catalyzed and microwave-assisted transformation.[23] The reactions are proposed to proceed through the azomethine ylide intermediates. [24]



Scheme 9. Syntheses of *N*-arylmethylindoles from indoline.

On the other hand, Pan *et al.* also reported the acid-catalyzed transformation of 2-carboxyindoline (**43**) into **42**.[25] In this section, we describe that **42** can be also obtained from **41** simply upon heating without catalyst, as our independent work.[26] Upon heating at 200 ˚C in an autoclave, indoline (**41**) reacts with arylaldehydes in toluene to give *N*-methylindoles (**42**). The results are shown in Table 2. Under the conditions, the pressure in the autoclave instrument was raised up to ca. 1.0 MPa. Although yields of **42f–42h** were relatively low, other *N*-substituted indoles **42a–42e** were obtained in moderate yields. The procedure is also simple an our pyrrole synthesis. However, this facile conversion is only limited in the reactions with arenecarbaldehydes. As mentioned above, Seidel claimed that the acid-catalyzed reaction proceeded through the azomethine ylide intermediates. The similar mechanism under our non-catalyzed reaction conditions is most probable. It is worthy to note that just upon heating *without catalyst* indoline reacts with arenecarbaldehydes to give *N*-arylmethylindoles.

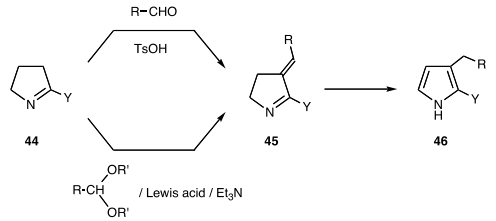
Table 2. Results of reactions of indoline with various arylcarbaldehydes under pressurized conditions without catalyst



Although yields of our experiments are slightly lower than those reported by Pan and Seidel *et al*., the procedure of our method is very simple.

2. 2,3-disubstituted pyrroles form 2-substituted pyrrolines

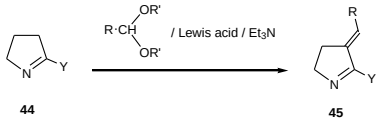
In this section, we describe development of another synthetic method for 2,3-disubstituted pyrroles **46** from easily accessible 2-substituted 1-pyrrolines **44**[27] via **45** (Scheme 10).[28]



Scheme 10. Synthesis of 2,3-disubstituted pyrroles from 2-substituted 1-pyrroline.

For the first step from **44** to **45**, it was found that a conventional aldol-type condensation of 2-phenyl-1-pyrroline (**44**; Y = Ar) with arylcarbaldehyde under continuous azeotropic distillation of water provided 3-arylidene-1-pyrroline (**45**; Y = Ar) in good yields. Besides, **45** could be obtained by the reactions of **44** with arylaldehyde dimethyl acetal assisted by a Lewis acid in the presence of triethylamine. Among the Lewis acids applied, such as $TiCl_4$, BF_3OEt_2, TMSOTf, and $SnCl_4$, $TiCl_4$ was found most effective to give the best yield of **45** (Table 3, entry 4). This reaction proceeds much faster than the conventional method, which requires a reaction time of a few days. Several 2-substituted 1-pyrrolines were subjected to condensation with some acetals under the most effective conditions. Benzaldehyde diethyl acetal reacted similarly, but the reaction proceeded slightly slower, giving **45** in a lower yield (Table 3, entry 5). Various dimethyl acetals such as dimethyl acetals of *p*-bromobenzaldehyde, *o*-tolualdehyde, 1-naphthalenecarbaldehyde, and 2-thiophenecarbaldehyde react with **44** to give **45** (Table 3, entry 6–13) and the yield mainly depends on the structure of the aryl group. Reactions of **44** with alkanal dimethyl acetals, such as dimethyl acetals of acetaldehyde and propanal, did not give any expected condensation products. None of the dimethyl ketals – acetone, benzophenone, acetophenone, and cyclohexane dimethyl ketals – reacts with **44** under the conditions. Reactions of other 2-(substituted phenyl)-1-pyrrolines provide satisfactory yields of **45** (Table 2, entries 6 and 7, respectively). However, **45** (Y = *t*-Bu, R = Ph) was obtained in low yield (Table 3, entry 12) probably because of the sterically bulky *t*-Bu group**.** Moreover, 2-(methoxycarbonyl)-1-pyrroline was found to be inactive under these conditions (Table 3, entry 13).

Table 3. Results of reactions of 1-pyrroline **44** with various arylcarbaldehyde acetals in the presence of Lewis acid in refluxing acetonitrile

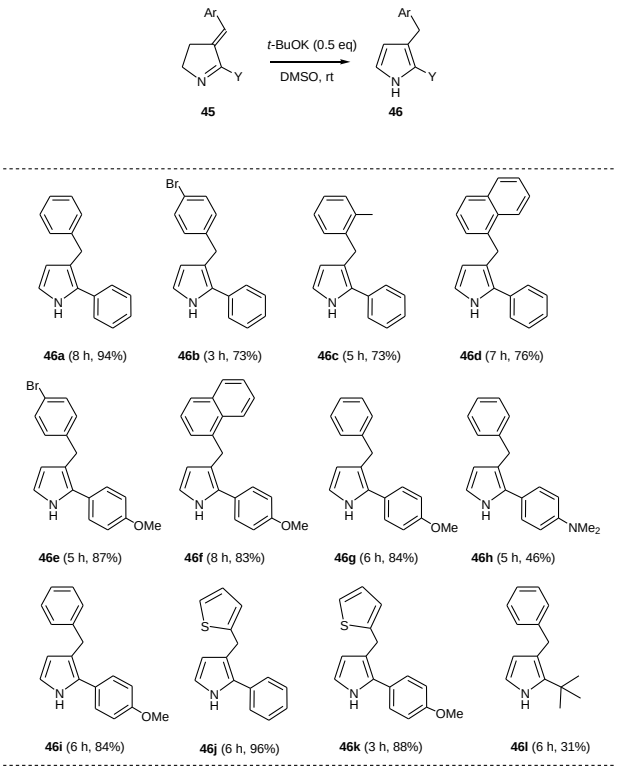


Entry	Y; R; R'	Lewis acid	Reacion time	Yield of **45** (%)
1	Ph; Ph; Me	F_3BOEt_2 (3 eq.)	22 h	30
2	Ph; Ph; Me	TMSOTf (3 eq.)	22 h	65
3	Ph; Ph; Me	$SnCl_4$ (3 eq.)	23 h	45
4	Ph; Ph; Me	$TiCl_4$ (3 eq.)	18 h	81
5	Ph; Ph; Et	$TiCl_4$ (3 eq.)	25 h	74
6	Ph; 4-Br-C_6H_4-; Me	$TiCl_4$ (3 eq.)	22h	70
7	Ph; 2-Me-C_6H_4-; Me	$TiCl_4$ (3 eq.)	12 h	41
8	Ph; 1-naphthyl; Me	$TiCl_4$ (3 eq.)	16 h	36
9	Ph; 2-thienyl; Me	$TiCl_4$ (3 eq.)	26 h	39
10	4-MeO-C_6H_4-; Ph; Me	$TiCl_4$ (3 eq.)	24 h	79
11	4-Me_2N-C_6H_4-; Ph; Me	$TiCl_4$ (3 eq.)	24 h	57
12	*t*-Bt; Ph; Me	$TiCl_4$ (3 eq.)	26 h	12
13	MeO_2C; Ph; Me	$TiCl_4$ (3 eq.)	26 h	0

Then, the second step, which is the base-catalyzed double-bond isomerization of pyrroline **45** to the corresponding pyrrole **46**, was examined. After preliminary examination under various conditions with several bases, under optimal conditions with *t*-BuOK/DMSO, pyrrolines **45** were converted to the corresponding pyrroles in good-to-high yields (Table 4). However, compounds **45** having the strong electron-donating groups at the 2 position were converted in low yields (**46h** and **46l**). This isomerization must proceed through repeated deprotonation and protonation steps. The electron-donating groups may reduce the acidity of the C–H bonds of **45**, and consequently decrease the yield of these reactions. Although substituents on pyrrole are limited, it has been demonstrated that various

2,3-substituted pyrroles could be synthesized form 1-pyrrolines by the facile two-step procedure.

Table 4. t-BuOK-catalyzed double-bond isomerization of 45.



3. Dipyrrin Synthesis Form 2,3-Disubstituted Pyrroles

Since the above-mentioned synthetic method for various disubstituted pyrroles was developed, we have focused to carry out our research for their application to novel functional dyes and fluorescent materials. In this section, a novel synthetic method for dipyrrins [29] from pyrroles obtained is described. The structure of dipyrrin can be found as a core carbon skeleton in 4,4-difluoro-4-bora-3a,4a

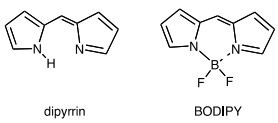
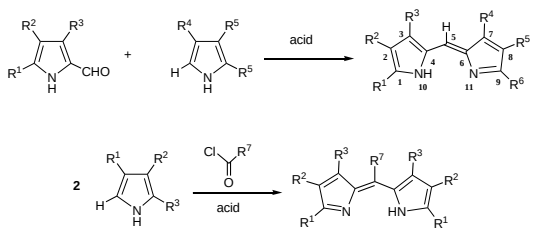
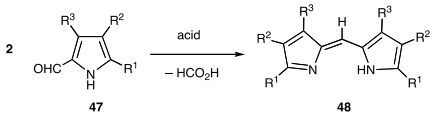


Figure 4. Structures of dipyrrin and BODIPY (4,4-difluoro-4-bora-3a,4a-diaza-*s*-indacene).

-diaza-*s*-indacene (BODIPY) dyes,[30] and some dipyrrins can be used as synthetic key intermediates for porphyrins and their analogs (Figure 4).[31] There have been reported many synthetic methods for dipyrrins. Among many previously reported synthetic methods for dipyrrins, reactions between pyrrole and pyrrole-2-carbaldehyde under acidic conditions and between pyrroles and acid chloride have been well documented (Scheme 11). In the former condensation, besides formation of **43**, dipyrrin **48** has often been reported to form in low yields (Scheme 12).[29] This deformylative condensation of **47** under acidic conditions is a minor process and, hence, the synthetic importance of this method has never been emphasized. Unexpectedly, we have found that the α-formyl derivatives of **47**, which can be obtained by formylation of **46**, undergo efficient condensation to give dipyrrins **48** in the presence of a Brønsted acid. [32–33] The results of the reactions from **47** to **48** are shown in Table 5. Although acetic acid was ineffective (entry 5–6), other stronger acids worked effectively to give dipyrrin **48a** in good to high yields. The highest yield was achieved by the way of entry 2. Under the same conditions of entry 2,



Scheme 11. Synthetic methods for dipyrrins by acid-catalyzed condensations.

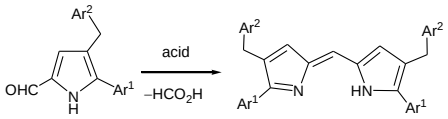


Scheme 12. Acid-catalyzed deformylative self-condensation of pyrrole-2-carbaldehyde.

48b–48d were obtained also in high yields (entry 8–10). A proposed reaction mechanism is shown in Scheme 13. The deformylation at the pyrrole ring[34] probably proceeds through the hydrate **49**, which undergoes protonation on the pyrrole ring to give **50**. Release of formic acid from **50** provides **46**, which reacts with **47** to give **51**. Finally, dehydration from **51** yields **48·H**$^+$. Indeed, it was independently confirmed that **46** reacts with **47** in HBr/AcOH at room temperature to give **48**. In contrast to the results of **47a–47d** having a *p*-anisyl group, **47e–47f** having a phenyl group behaves differently. Upon heating in refluxing HBr/AcOH, **48e–**

48f reacts slightly slower than **47a–47d**, resulting in the formation of a complex mixture.

Table 5. Acid-catalyzed deformylative self-condensation of 5-aryl-4-arylmethypyrrole-2-carbaldehyde

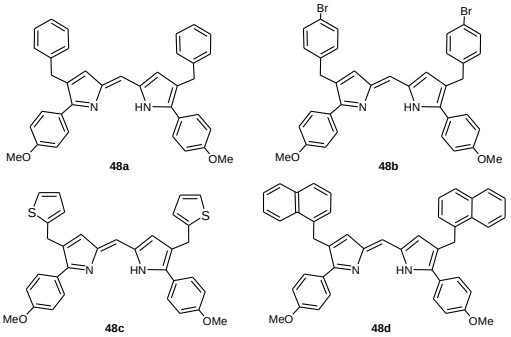


47 **48**

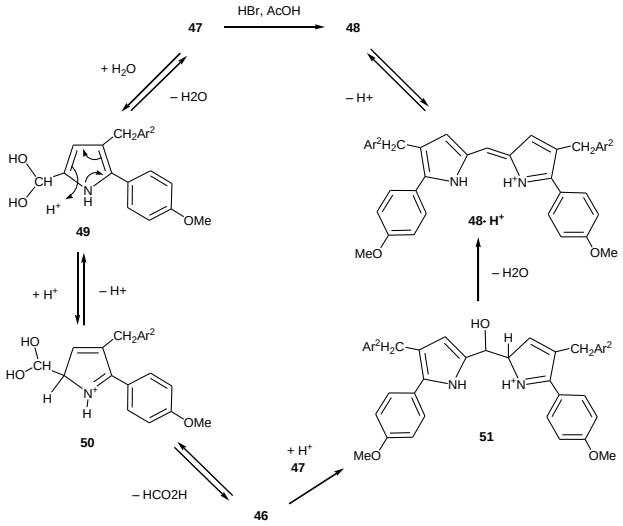
47a : Ar^1 = 4-MeO-C_6H_4-, Ar^2 = Ph
47b : Ar^1 = 4-MeO-C_6H_4-, Ar^2 = 4-Br-C_6H_4-
47c : Ar^1 = 4-MeO-C_6H_4-, Ar^2 = 2-thienyl
47d : Ar^1 = 4-MeO-C_6H_4-, Ar^2 = 1-naphthyl
47e : Ar^1 = Ph, Ar^2 = Ph
47f : Ar^1 = Ph, Ar^2 = 2-thienyl

Entry	**47**	Reaction Conditions	Yield of **48** (%) [a]
1	**47a**	HCl / AcOH (1/1), 95 ˚C, 3 h	**48a**;79
2	**47a**	HBr / AcOH (1/1), 85 ˚C, 4 h	**48a**; 93
3	**47a**	HBr / AcOH (1/1), 100 ˚C, 2 h	**48a**;84
4	**47a**	CF_3CO_2H / H_2O (9/1), 85 ˚C, 4 h	**48a**; 74
5	**47a**	AcOH / H_2O (9/1), 115 ˚C, 25 h	**48a**; trace (96)[b]
6	**47a**	AcOH / H_2O (9/1), 115 ˚C, 25 h	**48a**; 12 (74)[b]
7	**47a**	TsOH·H_2O (5 eq.) / toluene, reflux, 15 h	**48a**;70
8	**47b**	HBr / AcOH (1/1), 85 ˚C, 4 h	**48b**; 87
9	**47c**	HBr / AcOH (1/1), 85 ˚C, 4 h	**48c**; 88
10	**47d**	HBr / AcOH (1/1), 85 ˚C, 4 h	**48d**; 98
11	**47e**	HBr / AcOH (1/1), 85 ˚C, 6 h	**48e**; – [c]
12	**47f**	HBr / AcOH (1/1), 85 ˚C, 6 h	**48f**; –[c]

[a] Isolated yield after chromatography, [b] yield of recovery of **47** in parentheses, [c] no clear product was obtained.

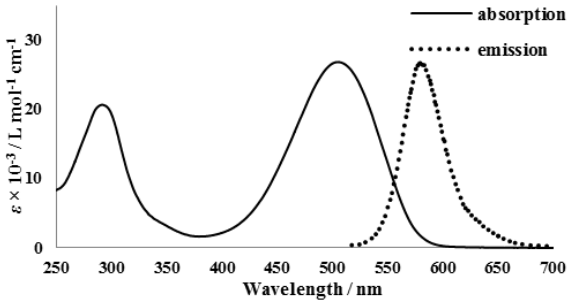


Although the existence of **48e–48f** in the reaction mixture can be deduced by ^{1}H NMR analysis, it could not be isolated from the mixture because of its low yield and particularly instability for SiO_2 chromatographic purification. Although the stability of **48e–48f** remains uncertain, it is possible that a methoxyl group of the aryl substituents at the 1,9 positions of **48a–48d** might contribute to their stability. The relatively higher reactivity of **47a–47d** in comparison with **47e–47f** in the reactions may be attributable to a more favorable protonation for **50** based on its increased π-electron density at the pyrrole ring induced by the *p*-anisyl groups.



Scheme 13. A proposed reaction mechanism for the formation of **48**.

Dipyrrins **48a–d** were obtained as red solids. They behave as a proton sensor in organic solvents.



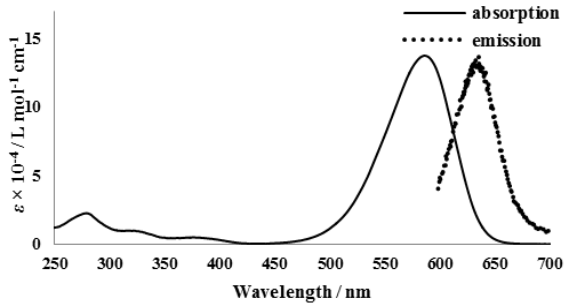


Figure 5. The UV-vis absorption and normalized emission spectra of **48a** in MeCN (top) and in 1%TFA-MeCN (bottom).

For example, the UV-vis and emission spectra of **48a** in acetonitrile **(**MeCN) and 1%CF_3CO_2H(TFA)-MeCN are shown in Figure 5. The absorption maximum at the visible region is observed at 504 nm in MeCN and at 586 nm in 1%TFA-CH_3CN. While the color of **48a** in a MeCN solution is red, it is blue in acidic media. The color change depending on concetration TFA in MeCN is shown in Figure 6. It is worthy to note that the color change of **48** is a contrast to that of Litmus paper, which shows red color in acid solutions.

0%TFA / CH_3CN ⟶ 10% TFA / CH_3CN

Figure 6. Color chanage of **48a** in TFA-MeCN.

The solid-state structure of **48a·H**$^+$ triflate salt was determined by X-ray analysis. ORTEP drawings are shown in Figure 7. The dipyrrin skelton of the X-ray structure is almost planar. Two C–C bonds around the meso carbon atom are 1.371 and 1.409 Å long. Although these lengths are between those of typical C–C single (1.54 Å) and double (1.34 Å) bonds, those are meaningfully different, that is, the dipyrrin part in the crystal structure has a bond alternation to some extent, apart from the complete resonance hybrid structure.

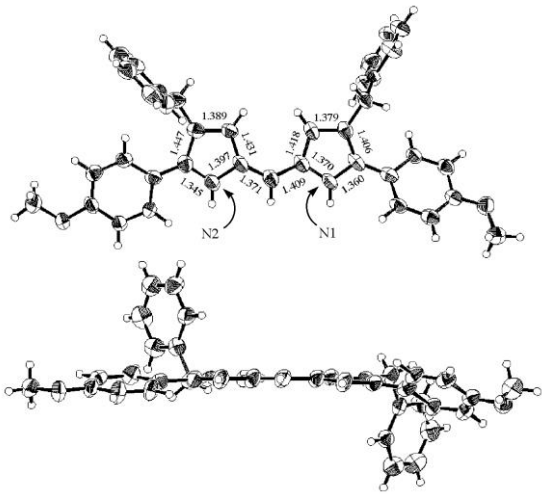
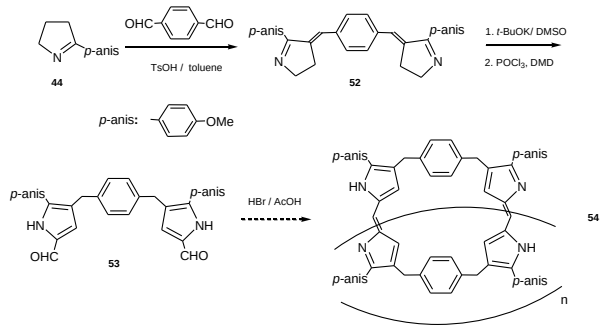


Figure 7. ORTEP drawings of **48a·HOTf**. Top view from the dipyrrin plane (top) and side view (bottom). Counter triflate anion and incorporated water were omitted for clarity. Numbers are bond lengths (in Å) of the dipyrrin part.

It has recently been found that dipyrrole dicarbaldehyde **53** can be easily obtained according to our pyrrole synthesis from terephthaldehyde. (Scheme 14). We are now studying oligomerizasion of **53** towards **54** having certain numbers of dypyrrin units in a macrocycle.



Scheme14. A synthetic plan towards oligodipyrrin **54**.

IV. CONCLUSION

We have found facile synthetic methods for various substituted pyrroles from pyrrolidine and 2-substituted 1-pyrrolines. In the one way, 1,3-disubstituted pyrroles **13** were synthesized by reaction of pyrrolidine and aldehyde. It is worthy to note that this reaction basically proceeds without any catalyst just by heating under pressurized conditions. On the other hand, 2,3-disubstituted pyrroles were synthesized from 2-substituted 1-pyrrolines by its aldol-type condensation with aldehyde and subsequent base-catalyzed double-bond isomerization. These results indicate that synthetic

ways from easily accessible five-membered nitrogen-containing compounds, such as pyrrolidine and 2-substituted 1-pyrrolines, to pyrroles are efficient and, hence, still important. Details of the two synthetic methods, their applications to synthesis of the pyrrolophane, and derivatization from the pyrroles obtained toward dipyrrins are described in this review. It is hoped that application and extension of our method for synthesizing pyrroles and dipyrrins contribute to developing novel pharmaceuticals and functionalized materials in near future.

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(29), 55 (33). HRMS Calcd for C20H27N 281.2143, found 281.2132.

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