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Organic Catalytic Multicomponent One-Pot Synthesis of Highly Substituted Pyrroles

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Abstract: A multicomponent synthesis of highly substituted pyrroles catalyzed by thiazolium salts has been disclosed. The reaction employs an acyl anion conjugate addition reaction of aldegyde and unsaturated ketones to generate 1,4-dicarbonyl compounds in situ. The subsequent addition of various amines promotes a Paal–Knorr reaction, affording the desired pyrrole nucleus in an efficient one-pot process.

Keywords: Highly substituted pyrroles, Paal–Knorr reaction, thiazolium salts catalysts

INTRODUCTION

The pyrrole heterocycle is an important structural attribute in many bioactive natural products,[1] therapeutic compounds,[2] and new organic materials.[3] Consequently, the efficient assembly of this class of molecule is a significant objective in synthetic chemistry. The construction of the pyrrole ring system typically involves a multistep approach from preformed intermediates, such as the classic Paal–Knorr cyclization reaction of 1,4-dicarbonyl compounds and amines.[4] More contemporary

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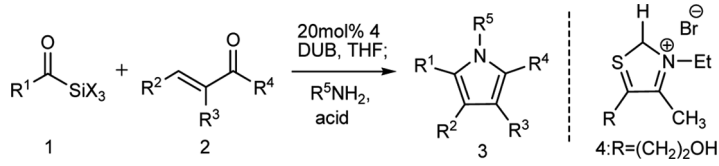


Scheme 1. Scheidt's general multicomponent pyrrole synthesis.

transition-metal-based strategies include the addition of chromium carbenes to dipolarophiles,[5a] the copper(I)-catalyzed cycloisomerization of alkynyl imines,[5b] and rhodium-catalyzed reactions, either N-H insertions[5c] or the combination of isonitriles and 1,3-diketones.[5d] However, an alternate and more direct strategy is the combination of multiple reactants in a single flask to afford the pyrrole core.

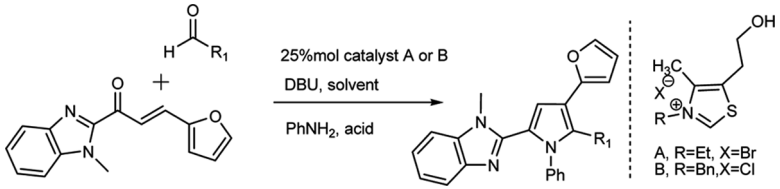
In 2004, Bharadwaj and Scheidt reported[6] a one-pot, multicomponent assembly of highly substituted pyrroles (**3**) utilizing a sila-Stetter/Paal–Knorr sequence of acylsilanes (**1**), unsaturated carbonyl compounds (**2**), and amines catalyzed by thiazolium salt (**4**) (Scheme 1).

However, they only focused on the starting material of expensive acylsilanes, and also in their paper the synthesis of only highy phenyl substituted pyrroles was reported. Herein, we report the realization of an improved one-pot, multicomponent assembly of not only highly phenyl but also highly heterocycle-substituted pyrroles utilizing a Stetter/Paal–Knorr sequence of cheaper and more common aldehydes (instead of acylsilabes), unsaturated carbonyl compounds, and amines catalyzed by thiazolium salt.

RESULTS AND DISCUSSION

At first, we found that under Bharadwaj and Scheidt's conditions, using aldehydes instead of acylsilanes, the pyrroles were the main products, but when we used heterocycle-substituted unsaturated ketones instead of phenyl unsaturated ketones, the yield was very poor. Perhaps the yield is poor because the heterocycle-substituted unsaturated ketones in the solvent of tetrahydrofuran (THF) are not very soluble. We found that the yield of the competitive reaction of 1,4-dikitones (benzoin condensation) is also very poor, which means there is much that can be improved in the reaction.

To improve the yield, we scanned different solvents and acid (Scheme 2). At last, we found that MeOH/HOAc is the best condition instead of THF/TsOH. The result is listed in Table 1.



Scheme 2. Highly heterocycle-substituted pyrrole synthesis in different conditions.

To study the efficiency of the procedure we found, we synthesized different heterocycle-substituted pyrroles (Scheme 3). The result is listed in Table 2.

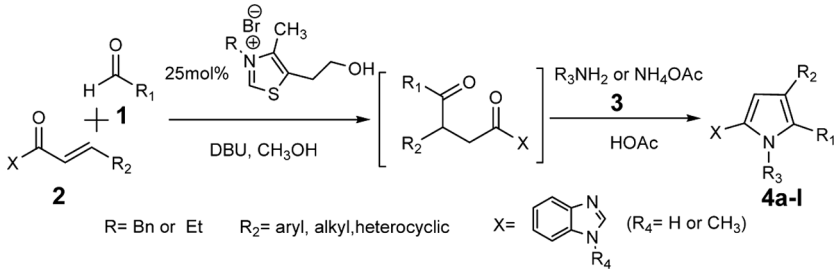
According to the literatures,[6] we also proposed the working catalytic cycle (Scheme 4). Our proposed working catalytic cycle involves the addition of a neutral carbene/zwitterionic species (**I**, generated in situ from the exposure of thiazolium salt **I** to DBU) to an aldehyde.[7] This nucleophilic attack of the carbonyl function of an aldehyde then generates the thiazolium salt adduct **II**. Deprotonation/reprotonation leads to the active aldehyde in the form of the resonance-stabilized enaminol-type Breslow intermediate **III**.[8] Then this nucleophilic acylation reagent **III** undergoes preferential addition to the more electrophilic α,β-unsaturated ketone. The resulting intermediate IV reforms the acyl anion carbonyl, which liberates the heterocyclic catalyst **I** and subsequently produces the 1,4-dicarbonyl compound V. Once the starting α,β-unsaturated ketone is consumed, the direct addition of a primary amine and acid to

Table 1. Highly heterocycle-substituted pyrrole synthesis in different conditions[a]

Entry	R_1	Solvent	Catalyst	Acid	Yield[b] (%)
1	Ph	THF	A	TsOH	20
2	Ph	1,4-Dioxane	A	TsOH	5
3	Ph	C_2H_5OH	A	TsOH	65
4	Ph	CH_3OH	A	TsOH	70
5	Ph	CH_3OH	A	HCl	60
6	Ph	CH_3OH	A	HOAc	75
7	propyl	CH_3OH	B	HOAc	70

[a]Reaction conditions: 25 mol% of A or B and 30 mol% of DBU and 10 mL methanol, reflux for 1–3 h. Amine and the acid were then added. The mixture was refluxed for an additional 1–3 h.

[b]Isolated yield after purification.



Scheme 3. Synthesis of pyrroles in the best condition.

the reaction followed by heating generates the desired pyrroles via the standard Paal–Knorr reaction manifold.

In conclusion, the process described herein is an efficient one-pot catalytic assembly of pyrroles via the thiazolium-catalyzed acyl anion conjugate addition of aldehyde. This approach utilizes a neutral organic molecule as a catalyst, is multicomponent in nature, and can rapidly install substitution at multiple positions of the pyrrole nucleus.

EXPERIMENTAL

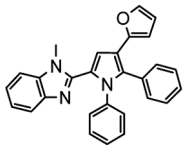
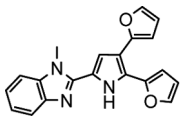
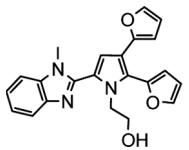
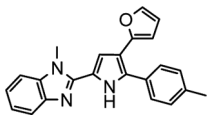
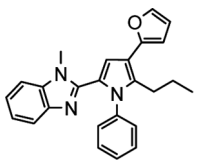
General Information

Melting points were obtained on a hot-plate microscope apparatus and were uncorrected. Infrared (IR) spectra were obtained on a Nicolet Fourier transform (FT)-IR 740 spectrometer in KBr discs. ^{1}H NMR (600 MHz) spectroscopies were recorded on a Bruker AV-600 spectrophotometer in $CDCl_3$ or dimethysulfoxide (DMSO-d_6).

Typical Experimental Procedure

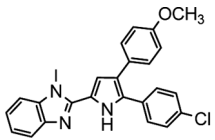
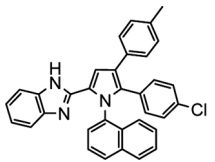
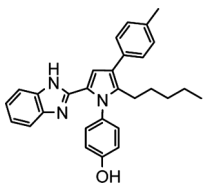
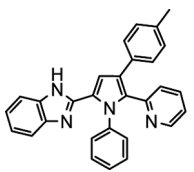
α,β-Unsaturated ketone (1.0 equiv), aldehyde (1.5 equiv), thiazolium salt (A or B 25 mol%), and DBU (30 mol%) were added to methanol, and the mixture was refluxed untill the completion of the reaction, which was indicated by thin-layer chromatography (TLC). After that, amine (2.0 equiv) and HOAc (3.0 equiv) were added to the solution. The solution was refluxed for another 1–3 h. After completion of the reaction, the reaction mixture was diluted with dichloromethane (20 mL) and washed with water (30 mL). The aqueous layer was washed with dichloromethane

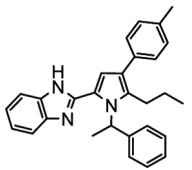
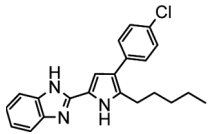
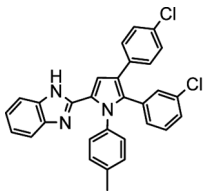
Table 2. Synthesis of pyrroles in the best condition[a]

Entry	R_1	R_2	R_3	R_4	Pyrroles		Yield[b] (%)
1	Phenyl	2-Furanyl	Phenyl	CH_3		4a	75
2	2-Furanyl	2-Furanyl	H	CH_3		4b	79
3	2-Furanyl	2-Furanyl	2-Hydroxyethyl	CH_3		4c	85
4	4-CH_3-Ph	2-Furanyl	H	CH_3		4d	73
5	Propyl	2-Furanyl	Phenyl	CH_3		4e	70

(*Continued*)

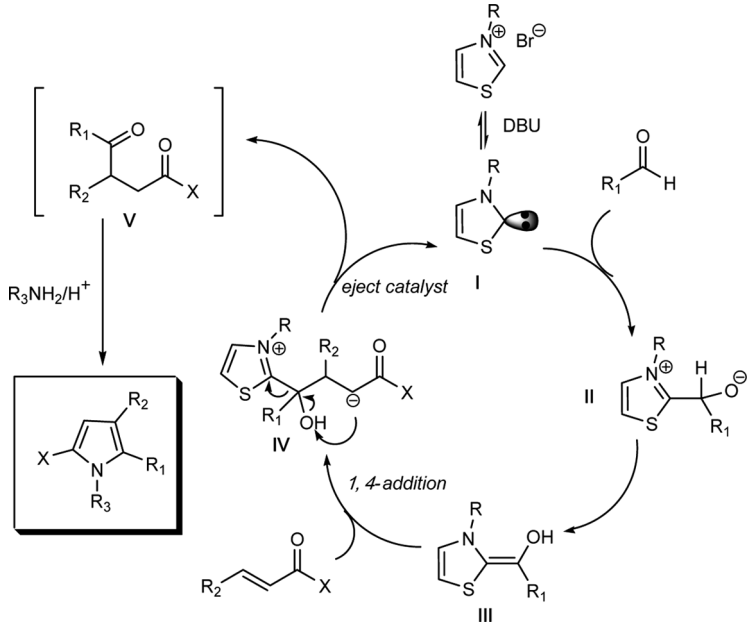
Table 2. Continued

Entry	R_1	R_2	R_3	R_4	Pyrroles	Yield[b] (%)
6	4-Cl-Ph	4-OCH_3-Ph	H	CH_3	 4f	70
7	4-Cl-Ph	4-CH_3-Ph	1-Naphthyl	H	 4g	66
8	Propyl	4-Cl-Ph	4-OH-Ph	H	 4h	79
9	2-Pyridinyl	4-CH_3-Ph	Phenyl	H	 4i	76

10	Propyl	4-CH_3-Ph	1-Phenylethyl	H		4j	56
11	Amyl	4-CH_3-Ph	H	H		4k	63
12	3-Cl-Ph	4-Cl-Ph	4-CH_3-Ph	H		4l	76

[a]Reaction conditions: 25 mol% of A or B and 30 mol% of DBU, 10 mL methanol, reflux for 1–8 h. Amine/NH_4OAc and HOAc were then added into the solution. The mixture was refluxed for an additional 1–3 h.

[b]Isolated yield after purification.



Scheme 4. Proposed catalytic cycle.

(3 × 10 mL) and dried over sodium sulfate. Removal of the solvent under reduced pressure followed by purification on silica gel (Merck, 100–200 mesh, ethyl acetate–hexane 1:5) afforded the corresponding pure highly substituted pyrroles.

Spectral Data for Selected Compounds

1-Phenyl-2-phenyl-3-(2-furanyl)-5-(1-methyl-benzimidazolyl)-1*H*-pyrrole (**4a**)

Off-white solid; mp 193–195°C; IR (KBr): 3041, 3049, 1596, 1496, 1445, 1399, 1324, 1281, 1244, 1071, 1005, 792, 741 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ: 3.5(s, 3H), 5.89 (s, 1H), 6.28 (s, 1H), 6.99 (d, $J = 5.59$ Hz, 2H), 7.07–7.08 (d, $J = 6.04$ Hz, 4H), 7.24–7.25 (m, 7H), 7.33–7.47 (m, 2H), 7.71–7.72 (d, $J = 6.04$ Hz, 1H); ^{13}C NMR (150 MHz, $CDCl_3$) δ: 30.9, 104.2, 107.7, 109.5, 111.0, 112.4, 115.3, 120.0, 122.2, 122.7, 127.3, 127.8, 128.1, 128.6, 128.9, 131.2, 1331.8, 132.9, 135.4, 137.9, 140.5, 146.4, 150.1.

2-(2-Furanyl)-3-(2-furanyl)-5-(1-methyl-benzimidazolyl)-1*H*-pyrrole (**4b**)

White solid, mp 232–235°C; IR (KBr): 3440, 3106, 2915, 2572, 1631, 1591, 1523, 1465, 1294, 1089, 1017, 824, 736 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ: 4.16 (s, 3H), 6.47 (s, 1H), 6.54 (s, 1H), 6.83 (d, $J = 2.81$ Hz, 1H), 7.36–7.37 (d, $J = 2.13$ Hz, 2H), 7.39–7.46 (m, 4H), 7.56 (s, 1H), 7.73–7.74 (d, $J = 7.67$ Hz, 1H), 13.07 (brs, 1H); ^{13}C NMR (150 MHz, $CDCl_3$) δ: 31.3, 105.7, 108.6, 109.2, 109.7, 110.4, 112.0, 112.3, 113.7, 114.6, 123.7, 124.3, 125.7, 128.2, 130.7, 139.4, 139.8, 141.0, 143.4, 146.0.

1-(2-Hydroxyethyl)-2-(2-furanyl)-3-(2-furanyl)-5-(1-methyl-benzimidazolyl)-1*H*-pyrrole (**4c**)

Brick red solid; mp 122–124°C; IR (KBr): 3421, 3202, 3111, 2845, 1603, 1563, 1449, 1401, 1365, 1324, 1076, 1014, 807, 741 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ: 3.98 (m, 5H), 4.35–4.36 (t, $J = 4.61$ Hz, 2H), 5.96 (d, $J = 2.97$ Hz, 1H), 6.34 (d, 1H), 6.57 (s, 1H), 6.65 (d, $J = 2.93$ Hz, 1H), 6.89 (s, 1H), 7.31–7.36 (m, 3H), 7.41–7.42 (d, $J = 7.67$ Hz, 2H), 7.61 (s, 1H), 7.77–7.78 (d, $J = 7.58$ Hz, 1H); ^{13}C NMR (150 MHz, $CDCl_3$) δ: 30.9, 47.3, 62.5, 103.7, 109.0, 109.7, 110.4, 112.3, 117.1, 118.5, 122.0, 122.1, 122.4, 122.5, 134.9, 139.8, 140.3, 142.7, 143.8, 144.8, 148.6.

2-(4-Methylphenyl)-3-(2-furanyl)-5-(1-methyl-benzimidazolyl)-1*H*-pyrrol (**4d**)

Brown solid; mp 123–125°C; IR (KBr): 3428, 2930, 1620, 1529, 1406, 1400, 1291, 1068, 1010, 826, 738 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ: 2.12 (s, 3H), 4.03 (s, 3H), 6.25 (d, $J = 2.31$ Hz, 1H), 6.39 (d, $J = 1.31$ Hz, Hz, 1H), 7.26 (s, 1H), 7.28–7.32 (m, 2H), 7.36–7.37 (d, $J = 7.05$ Hz, 1H), 7.39 (s, 1H), 7.47–7.49 (d, $J = 8.09$ Hz, 2H), 7.52–7.53 (d, 8.17 Hz, 2H), 7.69–7.70 (d, $J = 7.36$ Hz, 1H), 11.4 (brs, 1H); ^{13}C NMR (150 MHz, $CDCl_3$) δ: 21.5, 31.9, 105.2, 109.3, 111.1, 111.6, 114.7, 117.9, 120.9, 122.1, 123.0, 123.1, 130.1, 130.6, 131.5, 132.0, 135.6, 140.8, 145.9, 149.7.

2-(4-Chlorophenyl)-3-(4-methoxyphenyl)-5-(1-methyl-benzimidazolyl)-1*H*-pyrrole (**4f**)

White solid; mp 218–220°C; IR (KBr): 3448, 3062, 2935, 1604, 1517, 1477, 1405, 1288, 1248, 1173, 1096, 1025, 834, 744 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ: 3.83 (s, 3H), 4.12 (s, 3H), 6.85–6.87 (d, $J = 8.48$ Hz, 2H), 7.10–7.11 (d, $J = 8.48$ Hz, 1H), 7.21–7.22 (d,

$J = 8.47$ Hz, 2H), 7.29–7.31 (d, $J = 8.47$ Hz, 2H), 7.36–7.42 (m, 2H), 7.48–7.49 (d, $J = 8.04$ Hz, 1H), 7.59–7.61 (d, $J = 8.41$ Hz, 2H), 7.73–7.74 (d, $J = 7.90$ Hz, 1H), 13.00 (brs, 1H); ^{13}C NMR (150 MHz, $CDCl_3$) δ: 33.1, 55.3, 110.6, 113.7, 114.1, 118.8, 125.9, 126.1, 126.7, 128.6, 129.0, 129.5, 130.0, 130.1, 132.6, 134.4, 136.3, 142.2, 158.9.

1-(4-Hydroxyphenyl)-2-amyl-(4-methylphenyl)-5-(1-hydrogen-benzimidazolyl)-1*H*-pyrrole (**4h**)

White solid; mp 265–270°C; IR (KBr): 3430, 3170, 2960, 2925, 2864, 1641, 1555, 1508, 1467, 1328, 1228, 1181, 822, 741, 619 cm^{-1}; ^{1}H NMR (600 MHz, DMSO-d_6) δ: 0.85 (m, 3H), 1.28 (m, 4H), 1.70 (m, 2H), 2.34 (s, 3H), 2.79 (m, 2H), 7.12–7.66 (m, 13H), 12.36 (brs, 1H), 14.46 (brs, 1H).

1-Phenyl-2-(2-pyridinyl)-3-(4-methylphenyl)-5-(1-hydrogen-benzimidazolyl)-1*H*-pyrrole (**4i**)

White solid; mp 243–244°C; IR (KBr): 3430, 3054, 2875, 1625, 1590, 1499, 1458, 1458, 1404, 1344, 1274, 1225, 817, 745 cm^{-1}; ^{1}H NMR (600 MHz, $CDCl_3$) δ: 2.30 (s, 3H), 7.04–7.16 (m, 9H), 7.37–7.42 (m, 7H), 7.70–8.25 (m, 2H), 8.43 (brs, 1H); ^{13}C NMR (150 MHz, $CDCl_3$) δ: 21.1, 113.9, 122.0, 122.5, 125.7, 126.0, 126.8, 128.2, 128.8, 129.1, 129.2, 132.0, 133.7, 135.9, 138.5, 145.2, 149.3, 151.2.

1-(1-Phenylethyl)-2-propyl-3-(4-methylphenyl)-5-(1-hydrogen-benzimidazolyl)-1*H*-pyrrole (**4j**)

Yellow solid; mp 180–182°C; IR (KBr): 3422, 2963, 2870, 1589, 1500, 1443, 1406, 1338, 1275, 1223, 1118, 806, 748, 670 cm^{-1}; ^{1}H NMR (600 MHz, $CDCl_3$) δ: 0.66 (t, $J = 7.18$ Hz, 3H), 0.91–0.97 (m, 1H), 1.01–1.10 (m, 1H), 1.31–1.36 (m, 1H), 1.94–1.95 (d, $J = 7.12$ Hz, 2H), 2.36 (s, 3H), 2.55–2.58 (m, 2H), 6.77 (s, 1H), 7.02 (s, 1H), 7.16–7.17 (d, $J = 7.66$ Hz, 4H), 7.23–7.24 (d, $J = 7.60$ Hz, 3H), 7.29–7.33 (m, 4H), 7.68 (s, 1H), 8.89 (brs, 1H); ^{13}C NMR (150 MHz, $CDCl_3$) δ: 14.2, 19.6, 21.1, 23.0, 28.3, 53.4, 112.8, 121.9, 123.7, 126.2, 127.0, 128.6, 129.1, 133.9, 135.1, 135.3, 142.8, 146.6.

2-Amyl-3-(4-chlorophenyl)-5-(1-hydrogen-benzimidazolyl)-1*H*-pyrrole (**4k**)

White solid; mp 245–249°C; IR (KBr): 3423, 3179, 2924, 2866, 1641, 1561, 1523, 1469, 1329, 1271, 1229, 808, 741, 617 cm^{-1}; ^{1}H NMR

(600 MHz, DMSO-d_6) δ: 0.85 (m, 3H), 1.29 (m, 4H), 1.72 (m, 2H), 2.83 (m, 2H), 7.44–7.73 (m, 9H), 12.61 (brs, 1H), 14.88 (brs, 1H).

1-(4-Methylphenyl)-2-(3-chlorophenyl)-3-(4-chlorophenyl)-5-(1-hydrogen-benzimidazolyl)-1*H*-pyrrole (**4l**)

White solid; mp 226–228°C; IR (KBr): 3436, 3057, 2961, 1626, 1593, 1510, 1453, 1407, 1348, 1273, 1097, 822, 743 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ: 2.41 (s, 3H), 6.95–6.96 (d, $J = 7.48$ Hz, 1H), 7.06 (s, 1H), 7.10–7.12 (t, $J = 7.85$ Hz, 1H), 7.15–7.23 (m, 11H), 7.25 (m, 1H), 7.69 (s, 1H), 8.15 (brs, 1H); ^{13}C NMR (150 MHz, $CDCl_3$) δ: 20.5, 112.6, 121.8, 123.0, 124.9, 127.2, 127.8, 128.0, 128.5, 128.7, 129.6, 130.3, 131.2, 132.5, 132.6, 133.2, 134.3, 138.9, 144.2.

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