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Catalytic Multicomponent Synthesis of Highly Substituted Pyrroles Utilizing a One-Pot Sila-Stetter/Paal–Knorr Strategy

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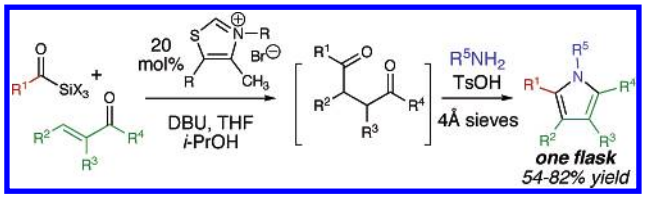
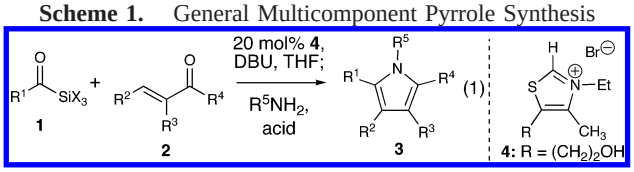
ABSTRACT



A multicomponent synthesis of highly substituted pyrroles catalyzed by thiazolium salts has been disclosed. The reaction employs an acyl anion conjugate addition reaction of acylsilanes (sila-Stetter) 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.

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 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. Herein, we report the realization of a one-pot, multicomponent assembly of highly substituted pyrroles (**3**) utilizing a sila-Stetter/Paal−Knorr sequence between acylsilanes (**1**), unsaturated carbonyl compounds (**2**), and amines catalyzed by thiazolium salt **4** (Scheme 1, eq 1).

Scheme 1. General Multicomponent Pyrrole Synthesis



Multicomponent reactions (MCRs) are becoming increasingly prevalent due to their improved efficiency, reduced waste, and rapid access of structural diversity.[6] In this vein, transition-metal-catalyzed MCRs have been developed for the synthesis of pyrroles.[7] However, as an alternative *organocatalytic* MCR approach,[8] we envisioned harnessing the thiazolium-catalyzed sila-Stetter reaction[9] to synthesize 1,4-dicarbonyl compounds in situ that can then be directly converted to pyrroles simply upon the addition of an amine.

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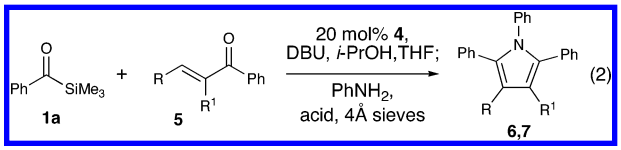
Notably, this single flask approach avoids transition-metal catalysts that can contaminate final compounds, employs readily available materials, and has the potential to directly install a number of elements of diversity around the pyrrole nucleus.

Our exploration of the feasibility of this one-pot reaction sequence relied on our development of the sila-Stetter reaction.[9] As a component of our comprehensive program investigating acylsilanes as efficient acyl anion precursors, we hypothesized that the Paal−Knorr cyclization conditions could be directly linked with our sila-Stetter process. The combination of an amine base (DBU, 1,8-diazabicyclo[5.4.0]-undec-7-ene) and commercially available thiazolium salt **4** produces the necessary nucleophilic zwitterionic catalyst in situ which promotes the acyl anion conjugate addition of acylsilane **1a**[10] to α,β-unsaturated ketones (**2**). To optimize the conversion of the resulting intermediate 1,4-dicarbonyl compound into the desired pyrrole structure, various reaction conditions were investigated (Table 1, eq 2).

Initially, a limited range of Brønsted acids was added directly to the reaction after consumption of the conjugate acceptor (**5**) followed by aniline and 4 Å molecular sieves (entries 1−4). Gratifyingly, after heating the reaction for an additional 8 h, the substituted pyrroles were isolated in moderate to good yields. The overall process is only mildly dependent on acid composition, with the best yield (70%, entry 5) obtained with *p*-toluenesulfonic acid (TsOH) and only 20 mol % of thiazolium precatalyst **4**. The observed one-pot, optimal yield for this sequential process indicates that the sila-Stetter and Paal−Knorr reactions are each ≥80% efficient on average. In addition, a tetrasubstituted pyrrole (C1−C4) can be accessed utilizing an α,β-disubstituted unsaturated ketone (entry 7).

Table 1. Optimization of Sila-Stetter/Paal−Knorr Reaction Conditions[a]

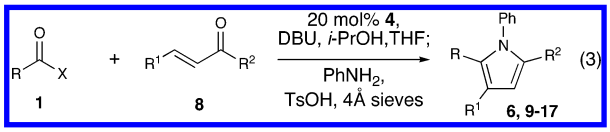


entry	R	R^1	acid	**4** (mol %)	yield[e] (%)	pyrrole
1	4Me-Ph	H	TFA[b]	30	52	**6**
2	4Me-Ph	H	H_2SO_4[c]	30	54	**6**
3	4Me-Ph	H	HCl[c]	30	63	**6**
4	4Me-Ph	H	TsOH[d]	30	62	**6**
5	4Me-Ph	H	TsOH[d]	20	70	**6**
6	4Me-Ph	H	TsOH[d]	10	48	**6**
7	Ph	COPh	TsOH[d]	20	35	**7**

[a] Reaction conditions: 20 mol % of **4** and 30 mol % of DBU (1,8-diazabicyclo[5.4.0]undec-7-ene), 4 equiv of *i*-PrOH; 0.8 M at 70 °C for 8 h. Amine, acid, and 4 Å sieves then added for an additional 8 h. See the Supporting Information for details. [b] 1 equiv. [c] Catalytic acid. [d] 2 equiv. [e] Isolated yield after purification.

With the optimal acyl anion addition/pyrrole formation conditions identified, the scope of this reaction sequence was examined (Table 2, eq 3). To this end, assorted acylsilanes and α,β-unsaturated ketones were employed with aniline added as the amine component. The process is tolerant of aryl acylsilanes (entries 1−3) as well as alkyl acylsilanes (entries 4 and 5). Additionally, the substituents on the silyl group can be either trialkyl ($SiMe_3$) or aryldialkyl ($SiPhMe_2$) without affecting conversion or yield. With regard to the electrophilic component, various aryl substituents can be incorporated onto the unsaturated ketone scaffold to afford good yields of the polyaromatic pyrroles (entries 6−10). Currently, α,β-unsaturated ketones possessing acidic protons

Table 2. Scope of the Sila-Stetter/Paal−Knorr Reaction[a]



entry	R	X	R^1	R^2	yield[b] (%)	pyrrole
1	Ph	$SiMe_3$	Ph	Ph	66	**9**
2	4-Me-Ph	$SiMe_3$	Ph	Ph	71	**10**
3	4-Cl-Ph	$SiMe_3$	Ph	Ph	61	**11**
4	cyclohexyl	$SiPhMe_2$	Ph	Ph	69	**12**
5	CH_3	$SiPhMe_2$	Ph	Ph	71	**13**
6	Ph	$SiMe_3$	4-Me-Ph	Ph	70	**6**
7	Ph	$SiMe_3$	3-Me-Ph	Ph	62	**14**
8	Ph	$SiMe_3$	4-Cl−Ph	Ph	58	**15**
9	4-Cl-Ph	$SiMe_3$	4-OMe-Ph	Ph	69	**16**
10	Ph	$SiMe_3$	Ph	4-Cl-Ph	80	**17**

[a] Reaction conditions: 20 mol % of **4** and 30 mol % of DBU, 4 equiv of *i*-PrOH; 0.8 M at 70 °C for 8 h. Amine, TsOH, and 4 Å sieves then added for an additional 8 h. [b] Isolated yield after purification.

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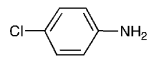
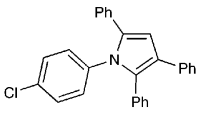
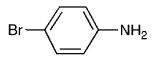
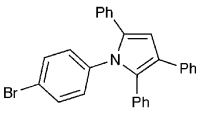
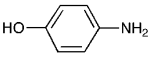
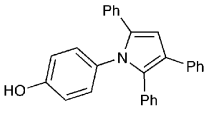
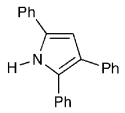
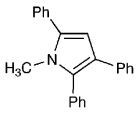
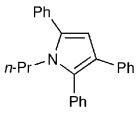
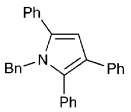
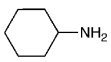
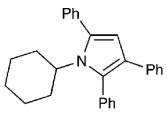
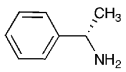
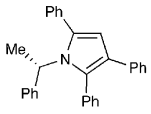
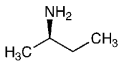
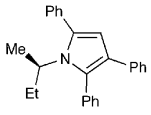
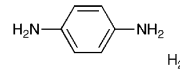
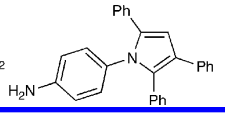
(10) For reviews on acylsilanes in organic chemistry, see: (a) Bonini, B. F.; Comes-Franchini, M.; Fochi, M.; Mazzanti, G.; Ricci, A. J. *Organomet. Chem.* **1998**, *567*, 181−189. (b) Cirillo, P. F.; Panek, J. S. *Org. Prepr. Proced. Int.* **1992**, *24*, 553−582. (c) Moser, W. H. *Tetrahedron* **2001**, *57*, 2065−2084. For a recent example of acylsilanes employed as acyl anions in the benzoin reaction, see: Xin, L. H.; Potnick, J. R.; Johnson, J. S. *J. Am. Chem. Soc.* **2004**, *126*, 3070−3071.

Table 3. Survey of Amines for Pyrrole Synthesis[a]

entry	Amine	pyrrole		yield (%)[b]
1			**18**	57
2			**19**	71
3			**20**	61
4	$H_4N{\cdot}O_2CCH_3$		**21**	62
5	CH_3NH_2		**22**	70
6	$CH_3(CH)_2NH_2$		**23**	82
7	$PhCH_2NH_2$		**24**	65
8			**25**	63
9			**26**	54
10			**27**	56
11			**28**	70

[a] Reaction Conditions: 20 mol % of **4** and 30 mol % of DBU, 4 equiv of *i*-PrOH; 0.8 M at 70 °C for 8 h. Amine, TsOH,and 4 Å sieves then added for an additional 8 h. [b] Isolated yield after purification.

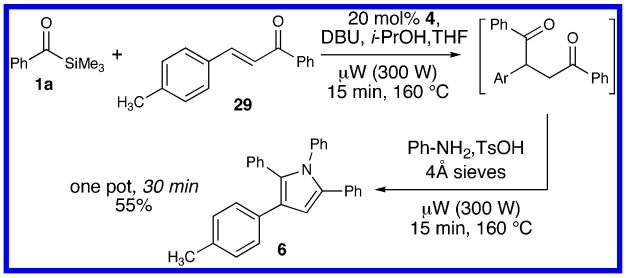
(e.g., (*E*)-1-phenylbut-2-en-1-one or (*E*)-4-phenylbut-3-en-2-one) do not proceed to 100% conversion and have not been examined fully in the context of this reaction.

The modularity of this pyrrole-forming reaction sequence is demonstrated by intercepting the 1,4-dicarbonyl compounds formed in situ with various amines (Table 3, eq 4). For example, substituted anilines are good nucleophiles for this reaction whether they are electron-rich or electron-deficient (entries 1−3). The direct addition of ammonium acetate to the reaction affords a good yield (62%) of the N−H pyrrole (entry 4). Unbranched primary amines such as methylamine (70% yield, entry 5) and benzylamine (65% yield, entry 7) along with branched primary amines (cyclohexylamine, entry 8, 63%) can be efficiently incorporated into the pyrrole framework. Additionally, optically active primary amines can be utilized for this reaction. Related chiral pyrrole compounds have been used in the synthesis of indolizidine alkaloids,[11] and they have been identified as highly selective potential treatments for diabetes.[12] The addition of (*S*)-α-methylbenzylamine or (*R*)-*sec*-butylamine affords the chiral pyrroles in moderate yield (entries 9 and 10). Interestingly, the controlled addition (1.5 equiv) of a diamine, such as 1,4-phenylenediamine, affords the monopyrrole in good yield (entry 11, 70%). This process has the potential to access unsymmetrical aryl-bridged bis-pyrroles, a class of compounds that show promise as new magnetic materials.[13]

Although this multihour process affords good yields of pyrroles, we felt that a more efficient means of heating could reduce the time required and thus improve the overall process. Gratifyingly, the use of microwave heating drastically reduces the reaction time.[14]

The first heating cycle for 15 min at 160 °C combines **1a** and α,*β*-unsaturated ketone **29** in the presence of 20 mol % **4**, 30 mol % DBU, and 4 equiv of 2-propanol. This sequence is followed by the addition of aniline and TsOH and a second 15 min heating cycle at 160 °C and smoothly affords the desired pyrrole (**6**) in 55% yield in only 30 min (Scheme 2). This streamlined approach generates the target heterocycle in 3% of the time required using conventional heating (30 min vs 16 h).

Scheme 2. Microwave-Assisted Sila-Stetter/Paal−Knorr Reaction



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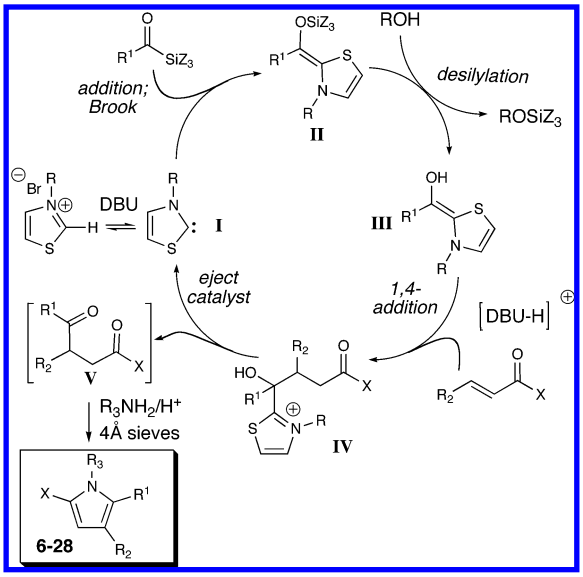
Our proposed working catalytic cycle (Scheme 3) involves the addition of a neutral carbene/zwitterionic species (**I**, generated in situ from the exposure of thiazolium salt **I** to DBU) to an acylsilane.[15] This nucleophilic addition initiates

Scheme 3. Proposed Catalytic Cycle



a 1,2-silyl group migration (Brook rearrangement)[16] and produces intermediate enolsilane **II**. The alcohol additive present in the reaction effectively desilylates **II**, thereby generating the "Breslow intermediate" **III**.[17] Due to the attenuated reactivity of the acylsilane, nucleophile **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, acid, and dehydrating agent (4 Å molecular sieves) to reaction followed by heating generates the desired pyrroles via the standard Paal−Knorr reaction manifold (**6**−**28**).

In conclusion, the process described herein is an efficient one-pot catalytic assembly of pyrroles via the thiazolium-catalyzed acyl anion conjugate addition of acylsilanes. 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. Further extensions of this sila-Stetter/heterocycle formation strategy and applications of these methodologies are underway and will be reported in future publications.

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Supporting Information Available: Experimental procedures and spectral data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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(15) For mechanistic discussions of the related thiazolium-catalyzed benzoin reaction, see: (a) Breslow, R.; Schmuck, C. *Tetrahedron Lett.* **1996**, *37*, 8241−8242. (b) Chen, Y. T.; Barletta, G. L.; Haghjoo, K.; Cheng, J. T.; Jordan, F. *J. Org. Chem.* **1994**, *59*, 7714−7722. (c) White, M. J.; Leeper, F. J. *J. Org. Chem.* **2001**, *66*, 5124−5131.

(16) (a) Brook, A. G.; LeGrow, G. E.; MacRae, D. M. *Can. J. Chem.* **1967**, *45*, 239−253. (b) Brook, A. G. *Acc. Chem. Res.* **1974**, *7*, 77−84.

(17) (a) Breslow, R. *J. Am. Chem. Soc.* **1958**, *79*, 3719−3726. (b) Breslow, R.; Kim, R. *Tetrahedron Lett.* **1994**, *35*, 699−702. The use of 3-octanol in the reaction affords 3-trimethylsilyloxyoctane (observed by gas chromatography), thus implicating the alcohol as the ultimate silyl acceptor.