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Ring-Opening Cyclization of Alkylidenecyclopropyl Ketones with Amines. An Efficient Synthesis of 2,3,4-Trisubstituted Pyrroles

Lianghua Lu,[†] Guofei Chen,[‡] and Shengming Ma*[,†,‡]

State Key Laboratory of Organometallic Chemistry, Shanghai Institute of Organic Chemistry, Chinese Academy of Sciences, 354 Fenglin Lu, Shanghai 200032, P. R. China, and Laboratory of Molecular Recognition and Synthesis, Department of Chemistry, Zhejiang University, Hangzhou 310027, P. R. China

masm@mail.sioc.ac.cn

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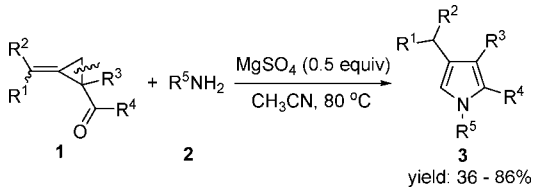
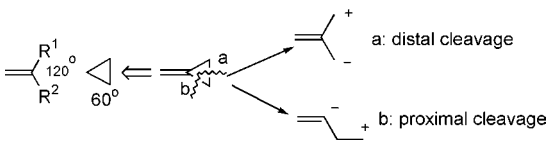
ABSTRACT



An efficient synthesis of 2,3,4-trisubstituted pyrroles via intermolecular cyclization of alkylidenecyclopropyl ketones with amines was observed. The addition of anhydrous $MgSO_4$ improved the yields of the products 3. A possible mechanism involving the distal cleavage of the C−C bond of cyclopropane ring was proposed.

Methylenecyclopropanes (MCPs) or alkylidenecyclopropanes are widely investigated because of the presence of an exocyclic carbon−carbon double bond and a strained three-membered carbocycle.[1,2] There are two types of ring opening of the cyclopropane, i.e., the distal cleavage (path a) and the proximal cleavage (path b) (Scheme 1). Thus, tuning of the highly selective ring opening of MCPs is an attractive research topic in organic synthesis.[3] Recently, our group reported the reactions of alkylidenecyclopropyl ketones under the catalysis of Pd(II), Pd(0), or I^- to afford different products via the cleavage of different C−C bonds in the ring depending on the nature of the catalyst and reaction conditions.[4] In our systematic study, we have observed the cycloisomerization of alkylidenecyclopropyl ketones via distal cleavage of the C−C bond of the cyclopropane ring under the catalysis of iodide.[4] On the basis of these previous results, we showed a strong interest in the intermolecular reaction of alkylidenecyclopropyl ketones with other

Scheme 1



nucleophilic reagents (Scheme 2). Pyrroles,[5] one class of the most important heterocyclic compounds, are not only important building blocks in the synthesis of natural products but also key structural unit in compounds with interesting biological activities.[6,7] Recently it was also found that pyrroles have broad application in the field of material

[†] Chinese Academy of Sciences.
[‡] Zhejiang University.

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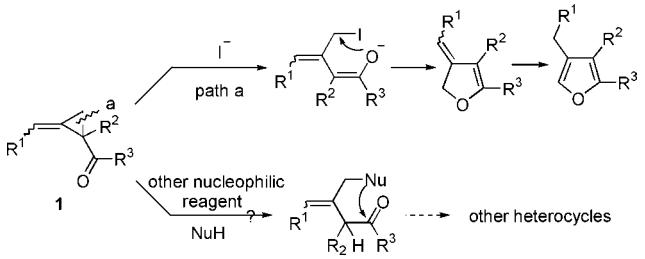
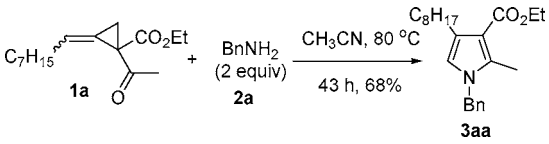
chemistry.[8] Hence, the efficient synthesis of pyrroles continues to be an active research area.[9,10] Herein we wish to report an efficient approach to 2,3,4-trisubstituted pyrroles via intermolecular cyclization of alkylidenecyclopropyl ketones with amines through distal cleavage of the carbon−carbon bond in the three-membered ring.

Scheme 2



In our initial study, we chose amine as the nucleophilic reagent replacing I^-. We were glad to find that the reaction of octylidenecyclopropyl methyl ketone **1a** and amine **2a** led to the formation of pyrrole **3aa** smoothly (Scheme 3). However, the reaction was slow in MeCN at 80 °C.

Scheme 3. Ring-Opening Cyclization of **1a** with **2a**



We optimized the reaction conditions by changing the amount of the amine and studied the solvent effect. From the results in Table 1, it should be noted that the reaction yield and rate were both improved when the amount of amine was increased to 4 equiv (entry 1, Table 1). Further investigation indicated that other solvents gave inferior yields (entries 2−5, Table 1) with the exception of DCE and dioxane, in which the reaction afforded the product **3aa** in similar yields with longer reaction times (entries 6 and 7, Table 1). Therefore, CH_3CN was the best solvent among these tested.

According to our primary understanding of this reaction, we thought that there should be one molecule of H_2O formed in the course of the reaction. Thus, the additives, which may be able to remove the in situ formed water, should promote the reaction. Some such representative results of the condition optimizations are listed in Table 2. It should be noted that

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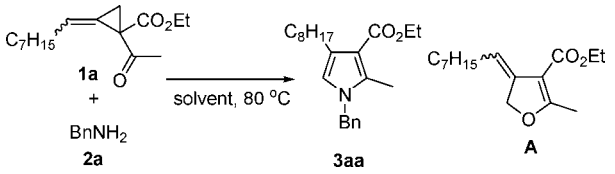
Table 1. Solvent Effects on the Intermolecular Cyclization of **1a** with **2a**[a]

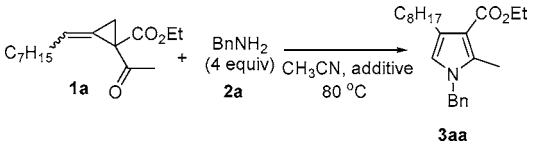


entry	solvent	time (h)	yield of **3aa** (%)[b]	recovery of **1a** (%)
1	CH_3CN	22	69	
2	toluene	49	40	15
3	DMF	14.5	36	
4	DME	41.5	65	1
5	THF	38.5	56	3
6	dioxane	38	69	2
7	DCE	28	69	

[a] The reaction was carried out using 0.25−0.5 mmol of **1a** and 4 equiv of **2a** in 1−2 mL of solvent at 80 °C under a N_2 atmosphere. [b] There was 2−14% of another product **A** formed via the cycloisomerization of **1a**.[4b]

product **3aa** was produced in 79% yield when 2 equiv of anhydrous $MgSO_4$ were added (entry 2, Table 2). Furthermore, the nitrogen atmosphere was not necessary (entry 3, Table 2). Further study showed that 0.5 equiv of anhydrous $MgSO_4$ was enough for a good yield of **3aa** (entry 8, Table 2). The best results were obtained when we used 4 equiv of benzylamine and 0.5 equiv of anhydrous $MgSO_4$ as additive in CH_3CN, leading to 78% yield of product **3aa** (entry 8, Table 2).

Table 2. Optimization of Intermolecular Cyclization of **1a** with **2a**[a]



entry	additive	N_2	time (h)	yield of **3aa** (%)
1	4Å MS	√	22.5	70
2	$MgSO_4$ (2 equiv)	√	22	79
3	$MgSO_4$ (2 equiv)		22	77
4	Na_2SO_4 (2 equiv)		22	64
5	$CuSO_4$ (2 equiv)		44	11
6	$MgSO_4$ (1.5 equiv)		20	78
7	$MgSO_4$ (1 equiv)		22	76
8	$MgSO_4$ (0.5 equiv)		22	78

[a] The reaction was carried out using 0.25−0.5 mmol of **1a** and 4 equiv of **2a** in 1−2 mL of CH_3CN under 80 °C.

With the optimized reaction conditions in hand, the scope of this reaction was explored, with some typical results summarized in Table 3. Several types of substituents R^1 such as an alkyl, benzyl, and TBS-protected hydroxyalkyl group could be introduced into the products **3** (entries 1−5, Table 3); R^4 can be an alkyl, phenyl, or strong electron-withdrawing

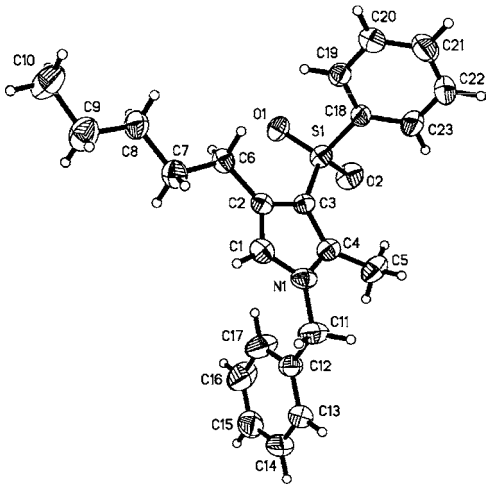
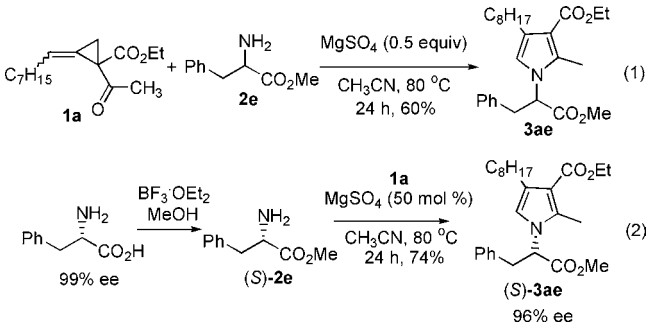


Figure 1. ORTEP representation of **3ha**.

group such as a trifluoromethyl group (entries 8−10, Table 3). When R^3 is H, the reaction also could be performed, but the reaction rate was quite slow (entry 11, Table 3). Moreover, different amines **2b**−**2d** were tested to afford corresponding products **3** in good yields (entries 10−15, Table 3). The structure of **3** was further confirmed by the X-ray diffraction study of **3ha** (Figure 1).[11]

Further investigation showed that the reaction of alkylidenecyclopropyl ketone **1a** and amino acid methyl ester **2e** afforded **3ae** in 60% yield (eq 1). This result indicated the possibility of the synthesis of chiral pyrrole derivatives. Inspired by this result, we investigated the reaction of chiral amino ester (*S*)-**2e**, which led to the product (*S*)-**3ae** in 74% yield with 96% ee (eq 2).



A rationale for this reaction is depicted in Scheme 4. There may be two possible pathways for the reaction. One may start from the intermolecular reaction of **1** and **2** to afford the cyclopropylimine intermediate **4** with realsing one molecule of H_2O (path a).[12] Cloke-type rearrangement of

(11) X-ray data for compound **3ha**: $C_{23}H_{27}NO_2S$, M_w = 381.52, monoclinic, space group *P*2(1)/*n*, Mo Kα, final *R* indices [$I > 2\sigma(I)$], R1 = 0.0535, wR2 = 0.0943, a = 10.9949 (13) Å, b = 8.8953 (11) Å, c = 21.764 (3) Å, α = 90°, β = 95.626 (3)°, γ = 90°, V = 2118.3 (4) Å^3, T = 293 (2) K, Z = 4, reflections collected/unique: 12112/4588 (R_{int} = 0.0969), parameters 247. CCDC 287334 contains the supplementary crystallographic data.

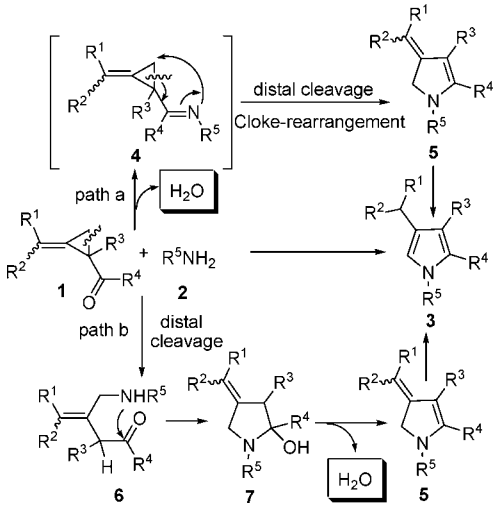
Table 3. Intermolecular Cyclization of Alkylidenecyclopropyl Ketones **1** with Amines **2** Affording 2,3,4-Trisubstitued Pyrroles **3**[a]

	1				2		
entry	R^1	R^2	R^3	R^4	R^5	time (h)	yield of **3** (%)
1	C_7H_{15}	H	COOEt	CH_3(**1a**)	Bn(**2a**)	22	78 (**3aa**)
2	C_4H_9	H	COOEt	CH_3(**1b**)	Bn(**2a**)	18.5	78 (**3ba**)
3	Bn	H	COOEt	CH_3(**1c**)	Bn(**2a**)	22	75 (**3ca**)
4	C_3H_6OTBS	H	COOEt	CH_3(**1d**)	Bn(**2a**)	16	77 (**3da**)
5	CH_3	C_2H_5	COOEt	CH_3(**1e**)	Bn(**2a**)	25	57 (**3ea**)
6	C_7H_{15}	H	$COCH_3$	CH_3(**1f**)	Bn(**2a**)	24	64 (**3fa**)
7	C_7H_{15}	H	SO_2Ph	CH_3(**1g**)	Bn(**2a**)	21	75 (**3ga**)
8	C_4H_9	H	SO_2Ph	CH_3(**1h**)	Bn(**2a**)	23.5	82 (**3ha**)
9	C_7H_{15}	H	COOEt	CF_3(**1i**)	Bn(**2a**)	26	40 (**3ia**)
10	C_7H_{15}	H	COOEt	Ph(**1j**)	*p*-MeOBn(**2b**)	63	67 (**3jb**)[b]
11	H	H	H	Ph (**1k**)	*p*-MeOBn(**2b**)	66	36 (**3kb**)[c]
12	C_7H_{15}	H	COOEt	CH_3(**1a**)	*p*-MeOBn(**2b**)	20	86 (**3ab**)
13	Bn	H	COOEt	CH_3(**1c**)	*p*-MeOBn(**2b**)	20	77 (**3cb**)
14	C_7H_{15}	H	COOEt	CH_3(**1a**)	*n*-C_4H_9(**2c**)	22	50 (**3ac**)
15	C_7H_{15}	H	COOEt	CH_3(**1a**)	*t*-C_4H_9(**2d**)	22	50 (**3ad**)

[a] The reaction was carried out using 0.25−0.5 mmol of **1**, 4 equiv of **2**, and 0.5 equiv of anhydrous $MgSO_4$ in 1−2 mL of CH_3CN at 80 °C. [b] 20% of the starting material **1j** was recovered. [c] 50% of the starting material **1k** was recovered.

intermediate **4** would easily lead to ring expansion via the subsequent nucleophilic attack of nitrogen atom at the less sterically hindered carbon atom in the cyclopropane ring, which would cause the distal cleavage to form the intermediate **5**.[13] Subsequent aromatization would afford the product **3**. Another possibility starts from the nucleophilic attack of the amine at the less sterically hindered carbon atom of the three-membered ring to afford intermediate **6** via distal cleavage (path b), which was similar to the way I^- reacts.[3e,4b,14,15] Then the nucleophilic nitrogen would attack the carbonyl group leading to 3-alkylidene-5-hydroxy tetrahydropyrrole intermediate **7**. Subsequent dehydration and aromatization would generate product **3** together with H_2O.

Scheme 4



In conclusion, we have developed an intermolecular cyclization reaction of alkylidenecyclopropyl ketones and amines, which provides an efficient route to 2,3,4-trisubstituted pyrroles. Further studies into the scope, mechanism, and synthetic application of this reaction are being carried out in our laboratory.

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Supporting Information Available: Typical experimental procedure and analytical data for all products not listed in the text, and file in CIF format. This material is available free of charge via the Internet at http://pubs.acs.org.

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