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An Efficient Route to 2-Substituted *N*-(1-Amino-3-methylpyrrol)amides by Ring-Opening Cyclization of Benzylidene- and Alkylidenecyclopropylcarbaldehydes with Hydrazides

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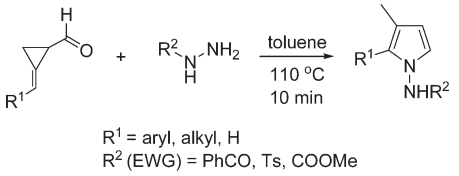
Received April 6, 2009



A convenient and efficient synthetic method for the construction of 2,3-disubstituted pyrrolamides in moderate to good yields is established. The in situ generated water significantly accelerates the reaction rate. A possible mechanism involving the cascade ring-opening and thermal-induced rearrangement to produce the five-membered ring is proposed.

Introduction

The pyrrole ring system is a useful structure in heterocyclic synthesis and displays a variety of important biological activities.[1] Although the pyrrolamides have broad applications in medicinal chemistry, only a few synthetic methods have been developed thus far.[2] Most of these methods relied on the Paal−Knorr condensation of 1,4-dicarbonyl compounds with hydrazine derivatives but in low yields.[3] Using exocyclic azolium ylide or other materials could also afford pyrrolamides but need multistep transformations.[4]

Methylenecyclopropanes (MCPs) are useful building blocks in organic synthesis due to their high level of reactivity derived from ring strain and easy availability.[5,6] During the last 10 years, Lewis acid and transition-metal-catalyzed reactions involving ring-opening of MCPs to form a variety of different carbocycles and heterocycles have been extensively investigated.[7] Recently, Lautens and co-workers have studied $MgCl_2$-catalyzed ring expansion of MCP hydrazones to form a class of isomeric cyclic diazadienes (Scheme 1a).[8]

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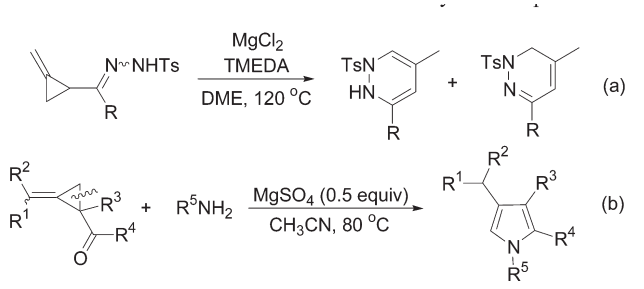
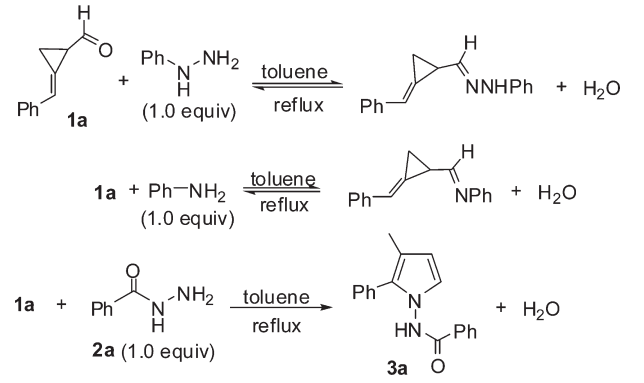
DOI: 10.1021/jo900730t Published on Web 07/17/2009

SCHEME 1. Previous Studies on the Formation of Heterocyclic Compounds from MCPs



SCHEME 2. Reaction of MCP Aldehyde 1a with Some Nucleophilic Reagents



In addition, Ma reported the reactions of alkylidenecyclopropyl ketones under the catalysis of Pd(II), Pd(0), or I^- to afford different furan or pyrrole derivatives[9] as well as an efficient synthesis of trisubstituted pyrroles via intermolecular cyclization of MCP ketones with amines (Scheme 1b).[10] Inspired by these previous research findings, we applied ourselves to investigate the intermolecular reactions of methylenecyclopropyl aldehydes with other heteroatom-containing compounds. Interestingly, though no reactions occurred upon treatment of MCP aldehydes (**1**) with phenylhydrazine and aniline, we found that benzhydrazide **2a** reacted with MCP aldehyde **1a** to generate a pyrrole product **3a** in good yield under reflux (Scheme 2). Therefore, we herein report a novel ring-opening and thermal-induced cyclization approach to a class of 2,3-disubstituted pyrrolamides.

Results and Discussion

We began our work by examining the reaction of **1a** with benzhydrazide **2a** at 110 °C in toluene catalyzed by Pd(0) (the Pd(0) species was in situ generated by $Pd(OAc)_2/Ph_3P$). It was found that substrate **1a** was consumed within 10 min (monitored by TLC plates), and a new product **3a** was formed in 53% yield (Table 1, entry 1). Further investigation revealed that the reaction proceeded smoothly upon heating at 110 °C without any catalyst, and the yield of **3a** increased to 76% (Table 1, entry 2). On the basis of previous literature and our primary understanding, we thought that one molecule of H_2O should be generated during the reaction process; thus, some drying agents were added to get rid of the in situ generated water. To our surprise, a much longer reaction time was required and the yield of **3a** did not increase significantly even when the employed amounts of **2a** were doubled, suggesting that the in situ generated water could significantly accelerate the reaction rate (Table 1, entries 3−5). Without any additive, **3a** could be produced in 83% yield within 10 min using 1.0 equiv of **1a** and 2.0 equiv of **2a** as substrates upon heating at 110 °C (Table 1, entry 6). Lowering the temperature to 80 and 100 °C afforded **3a** in 43% and 63% yield after a prolonged reaction time (60 and 30 min), respectively, indicating that the reaction temperature is also a crucial factor to this reaction (Table 1, entries 7 and 8). In the reaction of **1a** with 0.9 equiv of **2a** under otherwise identical conditions, the yield of **3a** was 76% (Table 1, entry 9).

Next, we continued to investigate the solvent effect of this reaction. The results are listed in Table 2. From tetrahydrofuran (THF) to dioxane, as the the reaction temperature rose, the yield of **3a** steadily increased from 18% to 52% (Table 2, entries 2−5). However, when the reaction was conducted at 130 °C in dimethyl sulfoxide (DMSO), **3a** was obtained only in 32% yield (Table 2, entry 6). Using *o*-xylene and *N*,*N*-dimethylformamide (DMF) as the solvents afforded **3a** in 68% yield at 130 °C and 78% yield at 140 °C, respectively (Table 2, entries 7 and 8). Carrying out the reactions in DMSO, *o*-xylene, and DMF at 110 °C produced **3a** in 22−63% yields, respectively (Table 2, entries 9−11). Therefore, toluene was the best solvent among all these solvents examined.

Having these optimized reaction conditions in hand, we next aimed to determine its reaction generality. We mainly chose benzhydrazide **2a** and 4-methylbenzenesulfonohydrazide **2b** as the substrates to react with various MCP aldehydes. The results of these experiments are summarized in Table 3. When the R^1 group was changed from aryl to alkyl or H, the reactions proceeded smoothly to afford the corresponding products **3** in moderate to good yields in most reactions of **1** with **2a** (Table 3, entries 1−10). When R^1 was aromatic group, the reactions of **1** with **2b** also proceeded smoothly to afford the corresponding products **4** in moderate to good yields whether electron-donating or electron-withdrawing substituent was introduced on the aromatic ring of **1** (Table 3, entries 1−8). However, in the cases of R^1 was alkyl group or hydrogen atom, complex product mixtures were formed (Table 3, entries 9 and 10). As for other hydrazides **2c**, **2d**, and **2e**, the corresponding products **3k**, **3l**, and **3m** were obtained in 93%, 69%, and 43% yields under the standard conditions, respectively (Table 3, entries 11−13). The yield of products **4** is lower than that of **3** under identical conditions presumably because compounds **4** are not very stable upon heating. Especially in the cases of **4i** and **4j**, the reaction was carried out at a relatively high temperature (110 °C), which may cause the decomposition of **4i** and **4j** during the reaction.

It should be noted that using (*Z*)-benzylidenecyclopropanecarbaldehyde **1k** as the substrate led to the same product **3b** in 75% yield as that of (*E*)-benzylidenecyclopropanecarbaldehyde (**1b**) as depicted in Scheme 3. Moreover, it was found that using hydrazine hydrate (**2f**) as the substrate to react with **1a** under the standard conditions produced the corresponding pyrrolamine product (**3n**) in 65% yield (Scheme 3).

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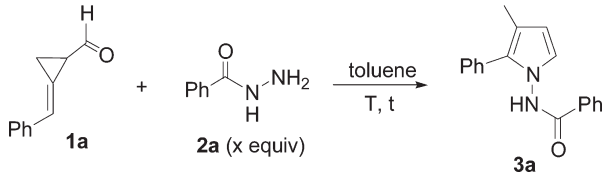
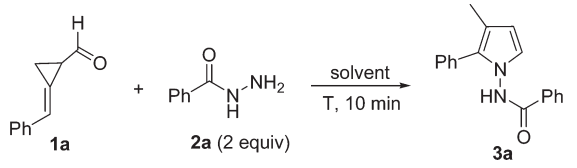
TABLE 1. Reaction of (*E*)-2-Benzylidenecyclopropyl Carbaldehyde (1a) with Benzhydrazide (2a) under Various Conditions[a]



entry	additive	*T* (°C)	time (min)	equiv	yield (%)[b] of **3a**
1	$Pd(OAc)_2$ (10 mol %)/PPh_3 (20 mol %)	110	10	1	53
2		110	10	1	76
3	4A MS	110	40	1	79
4	$MgSO_4$	110	30	2	76
5	4A MS	110	30	2	80
6		***110***	***10***	***2***	***83***
7		80	60	2	43
8		100	30	2	63
9		110	10	0.9	76[c]

[a]Reaction scale: 0.2 mmol of **1**. [b]Isolated yields. [c]0.22 mmol of **1a** and 0.2 mmol of **2a** were used.

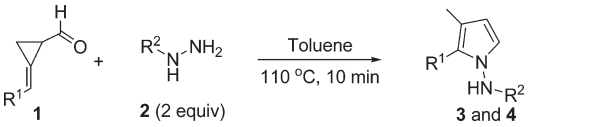
TABLE 2. Solvent Effect of the Reaction of (*E*)-2-Benzylidenecyclopropane Carbaldehyde (1a) with Benzhydrazide (2a)[a]



entry	solvent	*T* (°C)	yield (%)[b] of **3a**
1	toluene	110	83
2	THF	66	18
3	DCE	78	31
4	CH_3CN	80	36
5	1,4-dioxane	100	52
6	DMSO	130	32
7	*o*-xylene	130	68
8	DMF	140	78
9	DMSO	110	22
10	*o*-xylene	110	56
11	DMF	110	63

[a]Reaction scale: 0.2 mmol of **1a**. [b]Isolated yields.

TABLE 3. Reaction of Various Methylenecyclopropyl Carbaldehyde (1) with Different Hydrazides (2)[a]



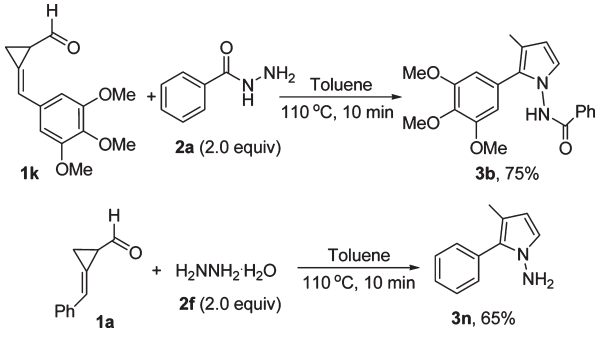
		yield (%)[b]		yield (%)[b]	
entry	R^1	R^2	**3**	R^2	**4**
1	**1a**,C_6H_5	**2a**, PhCO	**3a**, 83	**2b**, Ts	**4a**, 61
2	**1b**,3,4,5-$(MeO)_3C_6H_2$	**2a**, PhCO	**3b**, 89	**2b**, Ts	**4b**, 53
3	**1c**, *p*-MeC_6H_4	**2a**, PhCO	**3c**, 83	**2b**, Ts	**4c**, 75
4	**1d**, *m*-FC_6H_4	**2a**, PhCO	**3d**, 82	**2b**, Ts	**4d**, 62
5	**1e**, *p*-BrC_6H_4	**2a**, PhCO	**3e**, 64	**2b**, Ts	**4e**, 66
6	**1f**, *m*-MeC_6H_4	**2a**, PhCO	**3f**, 83	**2b**, Ts	**4f**, 58
7	**1g**, o-BrC_6H_4	**2a**, PhCO	**3g**, 72	**2b**, Ts	**4g**, 73
8	**1h**, *p*-ClC_6H_4	**2a**, PhCO	**3h**, 71	**2b**, Ts	**4h**, 56
9	**1i**, C_7H_{15}	**2a**, PhCO	**3i**, 79	**2b**, Ts	**4i**, –[c]
10	**1j**, H	**2a**, PhCO	**3j**, 32	**2b**, Ts	**4j**, –[c]
11	**1a**, C_6H_5	**2c**, MeOCO	**3k**, 93		
12	**1a**, C_6H_5	**2d**, $C_6H_5SO_2$	**3l**, 69		
13	**1h**, *p*-ClC_6H_4	**2e**, phthalic	**3m**, 43		

[a]Reaction scale: 0.2 mmol of **1**. [b] Isolated yields. [c]Complex product mixtures were obtained.

The product structures were determined by ^1H and ^{13}C NMR spectroscopy and HRMS or microanalyses. The crystal structure of **3m** was determined by X-ray diffraction, and its CIF data are presented in the Supporting Information.[11] A larger scale reaction using 0.5 mmol of **1a** and 1.0 mmol of **2a** as the substrates has been also carried out under the standard conditions, and it was found that **3a** was also obtained in 78% yield, suggesting that this reaction is also suitable on a larger scale.

On the basis of these results, a plausible mechanism for the formation of the pyrrole product is outlined in Scheme 4 using **1a** as a model. First, intermediate **A** is afforded by the intermolecular reaction of **1a** and **2a** along with the liberation of one molecule of H_2O. Then, a thermal-induced cyclization takes place to generate the five-membered cyclic intermediate **B**, which undergoes an isomerization to give the final product **3a**. At the present stage, we believe that the in situ generated imine intermediate is quite stable if it has an electron-withdrawing group (EWG), and it can undergo the next cyclization and isomerization upon heating.

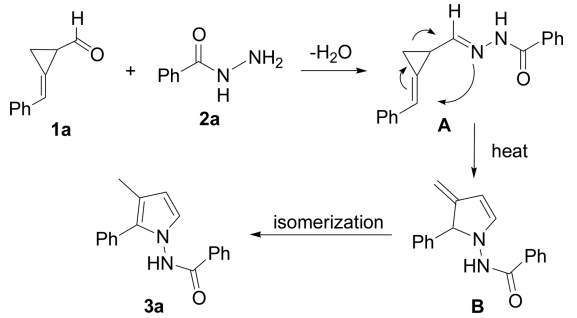
SCHEME 3. Further Determination of the Reaction Generality



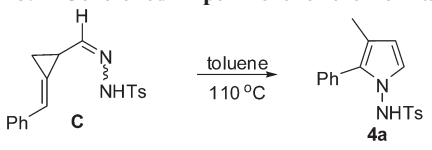
A control experiment was also performed to investigate whether intermediate **C** undergoes the reaction pathway to

(11) The crystal data of **3m** have been deposited with the CCDC (no. 713526).

SCHEME 4. Plausible Reaction Mechanism for the Formation of Product 3a

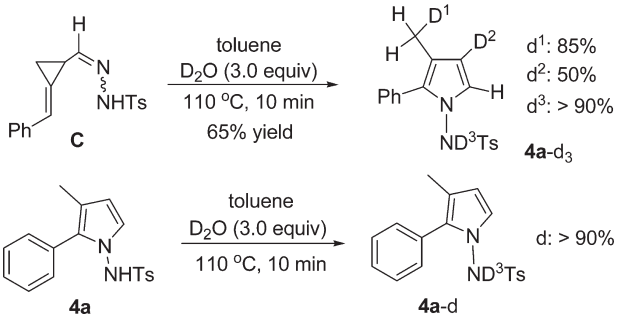


SCHEME 5. Controlled Experiment for the Formation of 4a



a: 61% yield, 1 h, without H_2O
b: 83% yield, 10 min, 2 equivalent of H_2O was added

SCHEME 6. Deuterium-Labeling Experiment in the Reaction and the Product



give the product **4a** (Scheme 5). We first prepared intermediate **C** by the reaction of **1a** with **2b** and then examined the transformation of **C** to product **4a** under the standard reaction conditions. It was found that the direct transformation of **C** to **4a** was sluggish but could be accelerated with the addition of 2.0 equiv of H_2O (Scheme 5).

A deuterium-labeling experiment was also conducted to validate our hypothesis using intermediate **C** as the substrate (Scheme 6). When 3.0 equiv of D_2O was added into the reaction system, it was found that besides sulfonamide NH moiety (D^3 content >90%), deuterium incorporation also occurred at methyl carbon (D^1 content 85%) and pyrrole skeleton (D^2 content 50%) based on ^1H NMR spectroscopic data (Scheme 6). Product **4a** can only undergo the H−D^3 exchange on the sulfonamide moiety upon treatment with D_2O under identical conditions (Scheme 6). The H−D^1 and H−D^2 exchange can take place in the conjugate enamine moiety in intermediate **A** (Scheme 4). The H−D^1, H−D^2, or H−D^3 exchange suggests that the extra H_2O can join the isomerization to accelerate the reaction rate by providing proton source to assist the transformation of intermediate **B** to product **3** or **4**. The results were consistent with our assumption.

In summary, a convenient and efficient synthetic method of disubstituted pyrrolamides **3** and **4** was developed from the reaction of **1** and **2** via a cascade ring-opening reaction and thermal-induced cyclization. The products **3** and **4** are important compounds in organic and medicinal chemistry. The potential utilization and extension of the scope of this synthetic methodology are currently under investigation.

Experimental Section

General Procedure for the Synthesis of 3a. MCP aldehyde **1a** (32.0 mg, 0.2 mmol), benzhydrazide **2a** (54.4 mg, 0.4 mmol), and toluene (2.0 mL) were added into a Schlenk tube. The reaction mixture was stirred at 110 °C for 10 min. The solvent was removed under reduced pressure, and then the residue was purified by a flash column chromatography.

***N*-(3-Methyl-2-phenyl-1*H*-pyrrol-1-yl)benzamide (3a):** white solid; mp 193−195 °C; ^1H NMR ($CDCl_3$, 300 MHz, TMS) δ 2.10 (s, 3H, CH_3), 6.11 (d, J = 3.0 Hz, 1H, CH), 6.64 (d, J = 3.0 Hz, 1H, CH), 7.24−7.37 (m, 7H, Ar), 7.46−7.51 (m, 1H, Ar), 7.60 (d, J = 7.5 Hz, 2H, Ar), 8.76 (s, 1H, NH); ^{13}C NMR ($CDCl_3$, 75 MHz, TMS) δ 12.2, 109.4, 116.0, 121.7, 127.1, 127.3, 128.2, 128.7, 129.6, 130.4, 130.9, 131.7, 132.3, 167.3; IR (CH_2Cl_2) ν 3261, 3059, 2922, 2865, 1665, 1602, 1524, 1488, 1281, 1214, 909 cm^{-1}; MS (EI) m/z 276 [M^+] (32.3), 173 (5.7), 171 (13.5), 115 (6.7), 106 (7.5), 104 (7.0), 77 (48.2), 51 (12.6). Anal. Calcd for $C_{18}H_{16}N_2O$: C, 78.24; H, 5.84; N, 10.14. Found: C, 78.23; H, 5.83; N, 10.20.

4-Methyl-*N*-(3-methyl-2-phenyl-1*H*-pyrrol-1-yl)benzenesulfonamide (4a): white solid; mp 170−172 °C; ^1H NMR ($CDCl_3$, 300 MHz, TMS) δ 1.95 (s, 3H, CH_3), 2.37 (s, 3H, CH_3), 6.01 (d, J = 3.0 Hz, 1H, CH), 6.77 (d, J = 3.0 Hz, 1H, CH), 6.82−6.84 (m, 2H, Ar), 6.99 (d, J = 8.4 Hz, 2H, Ar), 7.16−7.18 (m, 3H, Ar), 7.25 (d, J = 8.4 Hz, 2H, Ar), 7.64 (s, 1H, NH); ^{13}C NMR ($CDCl_3$, 75 MHz, TMS) δ 12.0, 21.6, 109.1, 116.6, 122.0, 126.5, 127.9, 128.0, 129.3, 129.4, 129.8, 130.2, 133.3, 144.4; IR (CH_2Cl_2): ν 3244, 3060, 2924, 2866, 1705, 1598, 1500, 1474, 1346, 1164, 1091 cm^{-1}; MS (EI) m/z 326 [M^+] (38.0), 171 (100), 156 (30.8), 144 (19.5), 115 (22.7), 91 (36.9), 77 (15.2), 65 (16.7); HRMS (EI) calcd for $C_{18}H_{18}N_2O_2S$ (M^+) requires 326.1089, found 326.1092.

Acknowledgment. We thank the Shanghai Municipal Committee of Science and Technology (08dj1400100-2), National Basic Research Program of China (973)-2009CB825300, and the National Natural Science Foundation of China for financial support (20472096, 20872162, 20672127, 20821002, and 20732008).

Supporting Information Available: Spectroscopic data (^1H, ^{13}C spectroscopic data), HRMS of the compounds shown in Tables 1 and 2, X-ray crystal structure of compound **3m**, and a detailed description of experimental procedures. This material is available free of charge via the Internet at http://pubs.acs.org.