1,4-Diazabicyclo[2.2.2]octane-Mediated Ring Opening of 1-Acetylcyclopropanecarboxamides and Its Application to the Construction of 3-Alkylated γ-Lactams

Ling Li,[a] Enxiang Wei,[a] Shaoxia Lin,[a] Bing Liu,[a] Fushun Liang*[a,b]

[a] Department of Chemistry, Northeast Normal University, Changchun 130024, P. R. of China
Fax +86(431)85099759; E-mail: liangfs112@nenu.edu.cn

[b] Key Laboratory for UV-Emitting Materials and Technology of Ministry of Education, Northeast Normal University, Changchun 130024, P. R. of China

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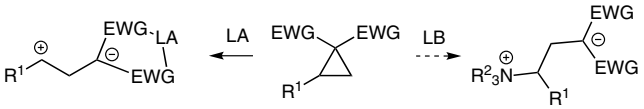
Abstract: 1,4-Diazabicyclo[2.2.2]octane (DABCO)-mediated ring opening of 1-acetylcyclopropanecarboxamides efficiently gave stable zwitterions that could be formed *in situ* or readily isolated. An application of this novel type of ring opening was demonstrated in a one-pot efficient construction of biologically interesting 3-alkyl γ-lactams. The Lewis-base protocol provides an opportunity for performing ring opening, cycloaddition, and rearrangement reactions of donor–acceptor cyclopropanes through organocatalysis.

Key words: Lewis bases, ring opening, cyclopropanes, lactams, chirality

Cyclopropane derivatives are useful in organic chemistry because they can undergo a variety of ring-opening reactions with a wide range of reactive species, such as electrophiles, nucleophiles, or radicals.[1] Recent decades have witnessed the development of Lewis acid catalyzed ring-opening reactions of cyclopropanes activated by electron donors and/or acceptors, which have found widespread applications in the construction of various carbocycles and heterocycles.[2] In the presence of a Lewis acid or a Brønsted acid, the activated cyclopropane can function as a source of 1,3-dipoles. However, there are few examples of Lewis base catalyzed ring-opening reactions of activated cyclopropanes.[3] As early in 1975, Danishefsky and Singh reported that a weak nucleophilic tertiary amine triggered ring opening of activated spiroacylal (6,6-dimethyl-5,7-dioxaspiro[2.5]octane-4,8-dione).[3a] In 2006, Kuznetsova and co-workers reported that 1,1-dinitrocyclopropanes react with tertiary amines such as triethylamine, pyridine, or 4-aminopyridine to give zwitterionic compounds.[3b] As a continuation of our previous researches on ring opening and recyclization of cyclopropanes activated by electron-withdrawing groups to give various heterocycles,[4] we aimed to explore the Lewis base catalyzed ring opening of activated cyclopropanes (Scheme 1). We surmised that the base protocol should provide a good opportunity for performing ring opening, cycloaddition, and rearrangement of donor–acceptor cyclopropanes through organocatalysis,[5] instead of by Lewis acid catalysis, as currently widely used.



Scheme 1 Lewis acid versus Lewis base mediated ring-opening reactions of activated cyclopropanes (EWG = electron-withdrawing group; LA = Lewis acid; LB = Lewis base)

Here, we report our most recent finding on ring-opening reactions of 1-acetylcyclopropanecarboxamides mediated by Lewis bases such as 1,4-diazabicyclo[2.2.2]octane (DABCO) or 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) to give zwitterionic intermediates that might be capable of functioning as sources of 1,3-dipoles,[6] and their further applications in a one-pot synthesis of 3-alkylated γ-lactams.[7]

We began our studies by using 1-acetyl-*N*-phenylcyclopropanecarboxamide (**1a**) as a model substrate for the reaction (Table 1). With triethylamine or 4-(*N*,*N*-dimethylamino)pyridine (1.05 equiv) as the Lewis base, no reaction occurred in acetonitrile at 60 °C (Table 1, entries 1 and 2). DBU induced deacetylation and cleavage of the cyclopropane ring (entry 3). To our delight, DABCO (1.05 equiv) efficiently induced ring opening of the activated cyclopropane **1a** to give the desired water-soluble zwitterionic salt **2a** in 94% yield (entry 4), demonstrating the validity of the Lewis-base concept. We then examined the effects of various organic solvents such as toluene, 1,2-dichloroethane, tetrahydrofuran, dimethyl sulfoxide, and *N*,*N*-dimethylformamide. All these solvents gave zwitterionic salt **2a**, but with reduced yields (entries 5–9). The use of water as a green solvent was also examined; as a result, salt **2a** was obtained in a 95% yield, comparable to that obtained in acetonitrile (entry 10). Increasing the temperature to 80 °C was unfavorable (entry 11), and reaction at 40 °C led to a prolonged reaction time and a decrease in the yield (entry 12).

Having identified the optimal conditions (Table 1, entry 10), we subjected various 1-acetylcyclopropanecarboxamides **1** to the reaction sequence (Scheme 2). The *N*-aryl

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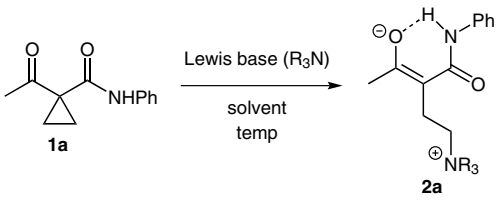
Table 1 Optimization of the Reaction Conditions[a]

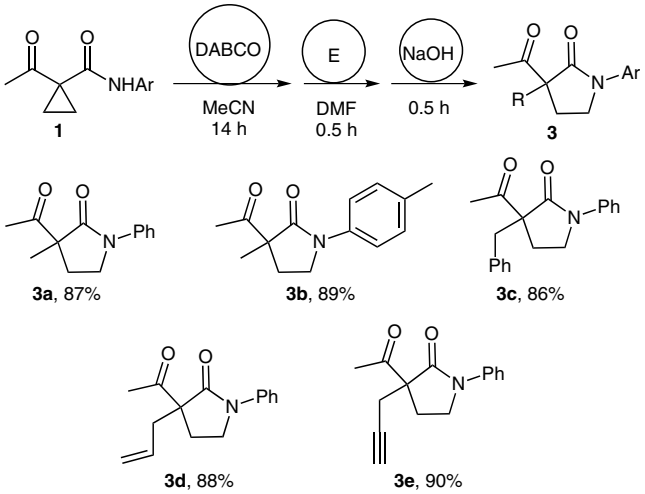


Entry	Lewis base	Solvent[b]	Temp (°C)	Time (h)	Yield[c] (%)
1	Et_3N	MeCN	60	24	NR
2	DMAP	MeCN	60	24	NR
3	DBU	MeCN	60	14	54[d]
4	DABCO	MeCN	60	14	94
5	DABCO	toluene	60	14	69
6	DABCO	DCE	60	14	70
7	DABCO	THF	60	14	81
8	DABCO	DMSO	60	14	86
9	DABCO	DMF	60	14	83
10	**DABCO**	**H_2O**	**60**	**12**	**95**
11	DABCO	H_2O	80	14	84
12	DABCO	H_2O	40	48	81

[a] Reaction conditions: **1a** (0.5 mmol), Lewis base (1.05 equiv), solvent (1.0 mL).
[b] Solvents were used directly as received.
[c] Isolated yield.
[d] Deacetylation was observed. The structure was not determined.

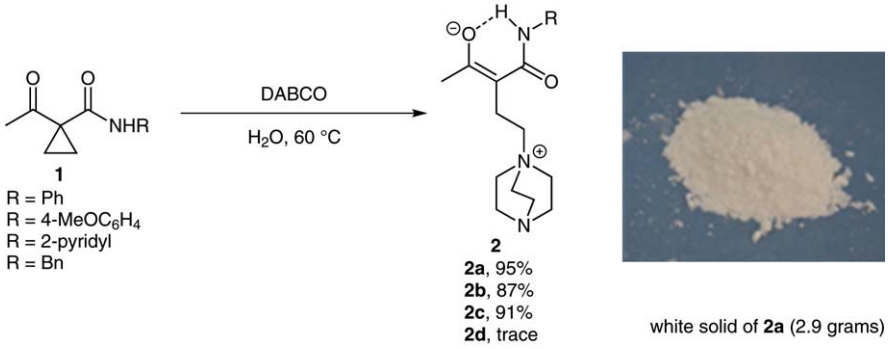
substrates **1a**–**c** successfully gave the corresponding zwitterions **2a**–**c** in 87–95% yields.[8] However, when R was an alkyl group such as benzyl, only trace amount of product **2** were obtained.[9] In addition to activation by the electron-withdrawing acetyl or amide groups, intramolecular hydrogen bonding is also likely to play a role in the ring opening of the cyclopropanes.[10] Note that zwitterion **2a** could be easily prepared as a white solid on a multigram scale.

Next, we examined potential applications of zwitterions **2**, which can be isolated or formed *in situ*. In a one-pot reaction starting from substrate **1a**, DABCO (1.05 equiv), iodomethane (1.5 equiv, used as an electrophile), and sodium hydroxide (1.2 equiv) were added sequentially (Scheme 3).[11] We were pleased to find that γ-lactam **3a**, with an all-carbon quaternary center, was obtained in 87% yield. On the basis of this result, we examined the reaction with three other electrophiles: benzyl bromide, allyl bromide, and propargyl bromide. 3-Acetyl-*N*-aryl-γ-lactams **3b**–**e** bearing a benzyl substituent, and latent ethylene and acetylene functional groups were successfully prepared as the sole products in 86–90% yields. Lactam **3b** was similarly prepared from the 4-tolyl analogue of **1a** in 89% yield.

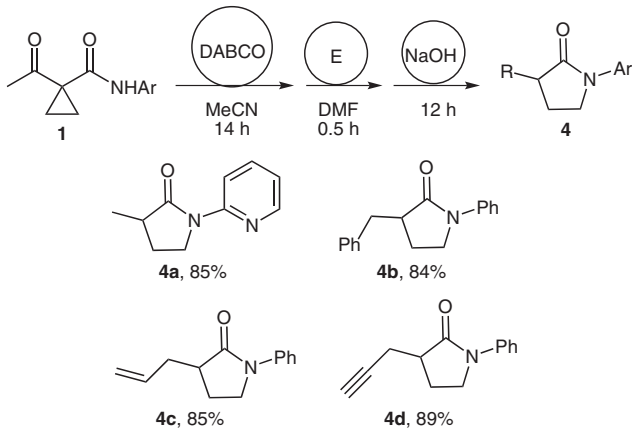


Scheme 3 Synthesis of γ-lactams **3** with a quaternary center. *Reagents and conditions*: (1) **1a** (Ar = Ph) or **1b** (Ar = 4-Tol) (0.5 mmol), DABCO (1.05 equiv), MeCN (1.0 mL), 60 °C, 14 h; (2) MeI, BnBr, CH_2=$CHCH_2Br$, or HC≡$CHCH_2Br$ (1.5 equiv), DMF (2.0 mL); r.t., 0.5 h; (3) NaOH (1.2 equiv), r.t., 0.5 h. Yields are isolated yields.

Moreover, deacetylation of compounds **3** occurred on increasing the concentration of base in the final step and prolonging the reaction time to 12 hours. We used this method to prepare the 3-substituted γ-lactams **4a**–**d** in high yields (Scheme 4).

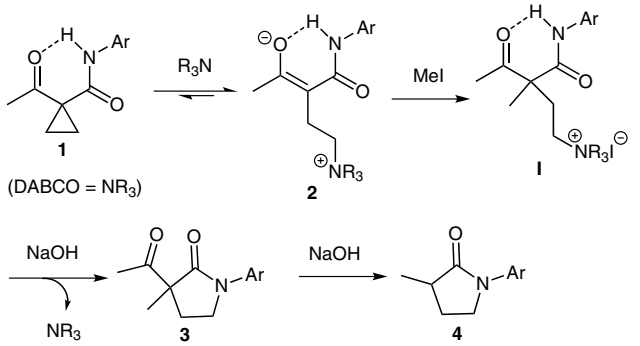


Scheme 2 DABCO-mediated ring opening of activated cyclopropanes **1** to give zwitterions **2**



Scheme 4 Synthesis of 3-substituted γ-lactams **4**. *Reaction conditions*: (1) **1a** (Ar = Ph) or **1c** (Ar = 4-Py) (0.5 mmol), DABCO (1.05 equiv), MeCN (1.0 mL), 60 °C, 14 h; (2) MeI, BnBr, CH_2=$CHCH_2Br$, or HC≡$CHCH_2Br$ (1.5 equiv), DMF (1.0 mL); r.t., 0.5 h; (3) NaOH (2.5 equiv), r.t., 12 h. Yields are isolated yields.

On the basis of these results, we proposed a possible mechanism for the formation of γ-lactams **3** and **4** (Scheme 5). The process involves tandem ring opening of the activated cyclopropane to give the zwitterionic intermediate **2**, enolate alkylation to give quaternary ammonium salt **I**, and intramolecular nucleophilic substitution to give γ-lactam **3**. Deacetylation occurs on prolonging the reaction time and increasing the base concentration, giving rise to 3-alkylated γ-lactams **4**.[12]



Scheme 5 Possible mechanism for the formation of γ-lactams **3** and **4**

In summary, DABCO-mediated ring opening of 1-acetylcyclopropanecarboxamides has been demonstrated. The resulting zwitterions, which can be isolated or used *in situ*, are readily obtained, even with water as the solvent. By a one-pot multistep reaction, 3-acetyl γ-lactams with an all-carbon quaternary center were prepared with high efficiency. 3-Alkylated γ-lactams can also be prepared by a subsequent deacetylation step. The Lewis base catalyzed ring opening, which has emerged as a new mode of activation, is expected to find additional applications in the cycloaddition and rearrangement reactions of donor–acceptor cyclopropanes. Further work is ongoing in our laboratory.

Acknowledgment

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(8) **(2*Z*)-3-(Anilinocarbonyl)-5-(4-aza-1-azoniabicyclo-[2.2.2]oct-1-yl)pent-2-en-2-olate (2a); Typical Procedure**
DABCO (156 mg, 1.05 equiv) was added to a solution of cyclopropane **1a** (102 mg, 0.5 mmol) in H_2O (1.0 mL), and the mixture was stirred at 60 °C for 12 h. The mixture was then cooled to r.t., and H_2O was removed under reduced pressure to give a white solid. The crude product was washed with MeOH and EtOAc (×3), and dried under ambient conditions to give a white solid; yield: 150 mg (95%); mp 173–175 °C; ^{1}H NMR (500 MHz, D_2O): δ = 1.75–1.76 (d, *J* = 7.5 Hz, 3 H), 2.32–2.35 (t, *J* = 8.0 Hz, 2 H), 2.72–2.75 (t, *J* = 8.5 Hz, 2 H), 2.79–2.80 (d, *J* = 6.5 Hz, 6 H), 3.01–3.02 (d, *J* = 6.5 Hz, 6 H), 6.83–6.86 (t, *J* = 7.0 Hz, 1 H), 7.11–7.14 (t, *J* = 8.0 Hz, 2 H), 7.25–7.26 (d, *J* = 8.0 Hz, 2 H); ^{13}C NMR (125 MHz, D_2O): δ = 20.4, 24.1, 44.2, 51.8, 63.7, 93.2, 119.9, 123.1, 129.5, 139.6, 170.0, 181.4; HRMS (ESI-TOF): *m/z* [M + H] calcd for $C_{18}H_{26}N_3O_2$: 316.2025; found: 316.2021.

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(11) **3-Acetyl-3-methyl-1-phenylpyrrolidin-2-one (3a); Typical Procedure**
DABCO (156 mg, 1.05 equiv) was added to a solution of cyclopropane **1a** (102 mg, 0.5 mmol) in MeCN (1.0 mL), and the mixture was stirred at 60 °C for 12 h. The mixture was then cooled to r.t., and MeCN was removed under reduced pressure. A solution of MeI (0.047mL, 1.5 equiv) in DMF (2.0 mL) was added, and the mixture was stirred at r.t. for 30 min. Finally, NaOH (240 mg, 1.2 equiv) was added, and the mixture was stirred for 30 min. The mixture was poured into brine (10 mL) and extracted with EtOAc (3 × 10 mL). The organic phases were combined, washed with H_2O (3 × 10 mL), dried ($MgSO_4$), filtered, and concentrated under reduced pressure. The crude product was purified by column chromatography (PE–Et_2O) to give colorless crystals; yield: 94.5 mg (87%); mp 86–88 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.55 (s, 3 H), 1.84–1.90 (m, 1 H), 2.33 (s, 3 H), 2.81–2.85 (m, 1 H), 3.71–3.75 (m, 1 H), 3.75–3.87 (m, 1 H), 7.16 (t, *J* = 7.0 Hz, 1 H), 7.49 (t, *J* = 7.5 Hz, 2 H), 7.63 (t, *J* = 7.5 Hz, 2 H); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 21.2, 26.0, 28.6, 45.8, 59.6, 119.8, 124.9, 128.8, 139.1, 172.4, 205.8; HRMS (ESI-TOF): *m/z* [M + H] calcd for $C_{13}H_{16}NO_2$: 218.1181; found: 218.1192.

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