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Copper-catalyzed cascade approach to 1,3-diazabicyclo[3.1.0]hex-3-enes from aziridines and ethyl diazoacetate

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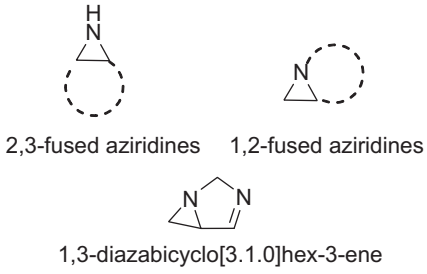
Dedicated to Professor Henry N. C. Wong on the occasion of his 60th birthday

ABSTRACT

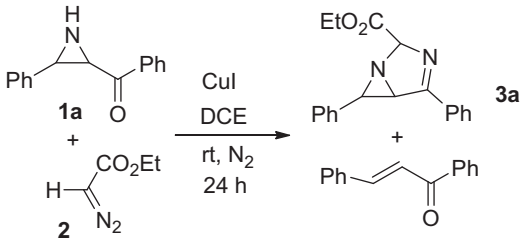
An efficient and general synthesis of 1,3-diazabicyclo[3.1.0]hex-3-enes via the copper-catalyzed cascade reaction of aziridines with ethyl diazoacetate is described.

Functionalized aziridines, with relatively reactive three-membered heterocycles, are potential precursors of many new biologically active compounds. They exist as substructures in a number of natural products and can be employed as efficient intermediates in the synthesis of other heterocyclic entities.[1] Zhu and Wu recently elegantly used aziridine as a lynchpin to construct antitumor antibiotic renieramycins M and G.[2] Promoted by active manganese, aromatic aziridine 2-carboxamides could be regioselectively transferred into 2-aminoamides.[3] With the ring opening of aziridines, a cascade reaction could thus be rationally designed and practically approached.[4] Aziridine-fused bicyclo compounds were also developed for the synthesis of pharmaceutical and natural products. However, most of these bicyclo compounds published in literature hitherto were 2,3-fused aziridines.[5] 1,2-Fused aziridines were seldom reported due to their unstability,[6] especially those aziridines fused to another heterocyclic ring, such as 1,3-diazabicyclo[3,1,0]hex-3-enes, which were ever synthesized by reaction of *trans*-2-aryl-3-aroylaziridines with aldehydes/ketones in alcoholic solutions saturated with ammonia in the presence of a small amount of ammonium bromide and found to be unstable to base and sensitive to sunlight.[7,8] As an improved approach leading to 1,3-diazabicyclo[3,1,0]hex-3-enes, Risitano et al. developed a three-component reaction of phenacyl chloride, aldehyde and ammonium acetate under microwave irradiation.[9]

As more aziridines and fused aziridines were identified with multipurpose applications, the development of a new methodology to construct aziridines and their derivatives has attracted more attention. As a remarkable contribution, fluoronium (F^+) was used as an organocatalyst for triggering the reaction between N-substituted imines and ethyl diazoacetate (EDA) to successfully afford aziridines.[10] Illuminated by this work and as a part of our ongoing research using aziridine as a lynchpin in cascade reactions,[6,11] we herein report a copper-catalyzed reaction between 2-aryl-3-aroylaziridines and EDA, which efficiently furnished 1,3-diazabicyclo-[3,1,0]hex-3-ene.



Initially, we examined the reaction between aziridine **1a** and EDA (**2**) using 10 mol % CuI as catalyst. As shown in Scheme 1, the reaction gave 1,3-diazabicyclo[3,1,0]hex-3-ene **3a** along with chalcone when an excess amount of EDA was used. We then opti-



Scheme 1. Reaction between aziridine **1a** and EDA (**2**).

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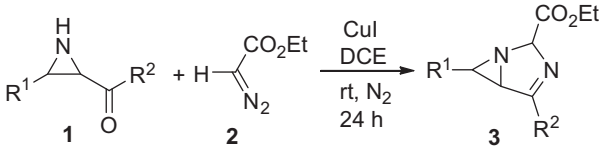
Table 1
Effect of reaction conditions on the copper-catalyzed reaction of **1a** and **2**[a]

Entry	Catalyst (equiv)	**1a**/**2**	Reaction temperature (°C)	Solvent	Yield[b] (%)
1	CuCl (0.1)	1:2	25	DCE	46
2	CuBr (0.1)	1:2	25	DCE	49
3	CuCN (0.1)	1:2	25	DCE	44
4	CuI (0.1)	1:2	25	DCE	58
5	CuI (0.1)	1:2	25	THF	53
6	CuI (0.1)	1:2	25	CH_3CN	0
7	CuI (0.1)	1:2	25	Toluene	42
8	CuI (0.1)	1:2	0	DCE	0
9	CuI (0.1)	1:2	50	DCE	50
10	CuI (0.05)	1:2	25	DCE	48
11	CuI (0.2)	1:2	25	DCE	55
12	CuI (0.1)	1:1	25	DCE	42
13	CuI (0.1)	1:1.5	25	DCE	56

[a] Reaction conditions: **1a** (0.5 mmol), **2** (0.5, 0.75 or 1.0 mmol), solvent (5 mL), 24 h.
[b] Isolated yield refers to aziridine **1a**.

Table 2
Scope for the copper-catalyzed reaction of aziridines with EDA[a]



Entry	R^1/R^2	Product	Yield[b] (%)
1	C_6H_5/C_6H_5 (**1a**)	**3a**	58
2	4-ClC_6H_4/C_6H_5 (**1b**)	**3b**	54
3	4-BrC_6H_4/C_6H_5 (**1c**)	**3c**	56
4	4-PhC_6H_4/C_6H_5 (**1d**)	**3d**	78
5	3-$MeOC_6H_4/C_6H_5$ (**1e**)	**3e**	76
6	4-$MeOC_6H_4/C_6H_5$ (**1f**)	**3f**	70
7	C_6H_5/4-$MeOC_6H_4$ (**1g**)	**3g**	72
8	3-$MeOC_6H_4$/4-$MeOC_6H_4$ (**1h**)	**3h**	61
9	4-ClC_6H_4/4-$MeOC_6H_4$ (**1i**)	**3i**	65
10	1-Naphthyl/C_6H_5 (**1j**)	**3j**	55
11	2-Furyl/C_6H_5 (**1k**)	**3k**	41
12	C_6H_5/*t*-Bu (**1l**)		NR

[a] Reaction conditions: **1** (0.5 mmol), **2** (1.0 mmol), CuI (0.05 mmol), DCE (5 mL), 24 h.
[b] Isolated yield refers to aziridine **1**.

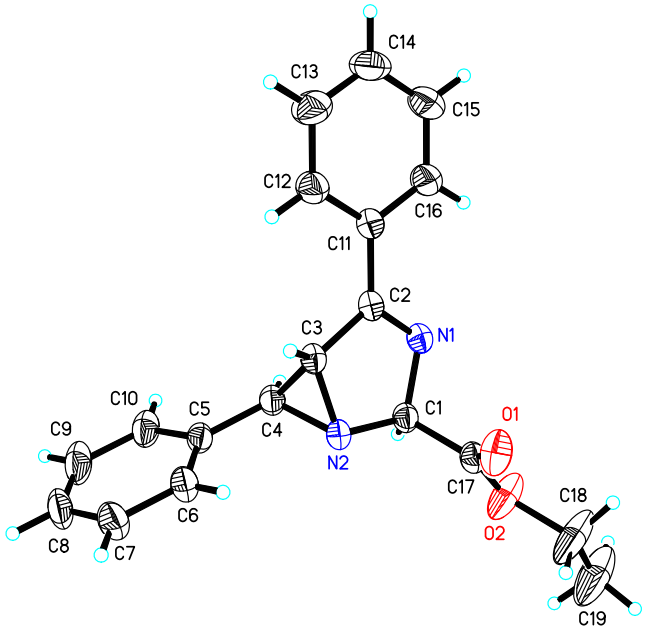
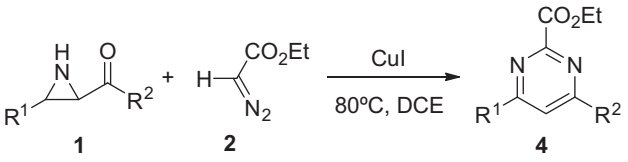


Figure 1. X-ray structure of compound **3a**.

mized the reaction conditions and the results are summarized in Table 1. CuI was observed to be the best copper (I) source in comparison with others, such as CuCl, CuBr, and CuCN (Table 1, entries 1–4), whereas dichloroethane (DCE) was found to be a suitable solvent (Table 1, entries 4–7). Besides these two key factors, the yield also depended on the reaction temperature (Table 1, entries 4, 8 and 9) and the amount of catalyst (Table 1, entries 4, 10 and 11) as well. Decreasing the amount of EDA led to relatively lower yields (Table 1, entries 12 and 13). Thus, we selected CuI as the catalyst, dichloroethane as the solvent and ran the reaction mixture at 25 °C for 24 h. Under this condition, the highest yield of **3a** (58% yield) was obtained (Table 1, entry 4). It must be indicated that the vice-product chalcone was also obtained in almost similar yield with the desired product **3a**. For entry 4 in Table 1, chalcone was isolated in 51% yield (58% yield for **3a**). This vice-product could be recycled for preparation of the starting material **1a**.[12]

With the optimized reaction conditions in hand, we next focused our attention on the diversity of aziridines**1**.[12] As shown in Table 2, both phenyl-substituted aziridines **1a–i** (Table 2, entries 1–9) and 1-naphthyl-substituted aziridine **1j** (Table 2, entry 10) gave the desired 1,3-diazabicyclo[3,1,0]hex-3-enes **3a–j** in moderate to good yields (54–78%), while furyl-substituted aziridine **1k** afforded **3k** in a relatively lower yield (41%) (Table 2, entry 11).[13] For the electronic effect of R^1 and R^2 groups in aziridines **1**, it

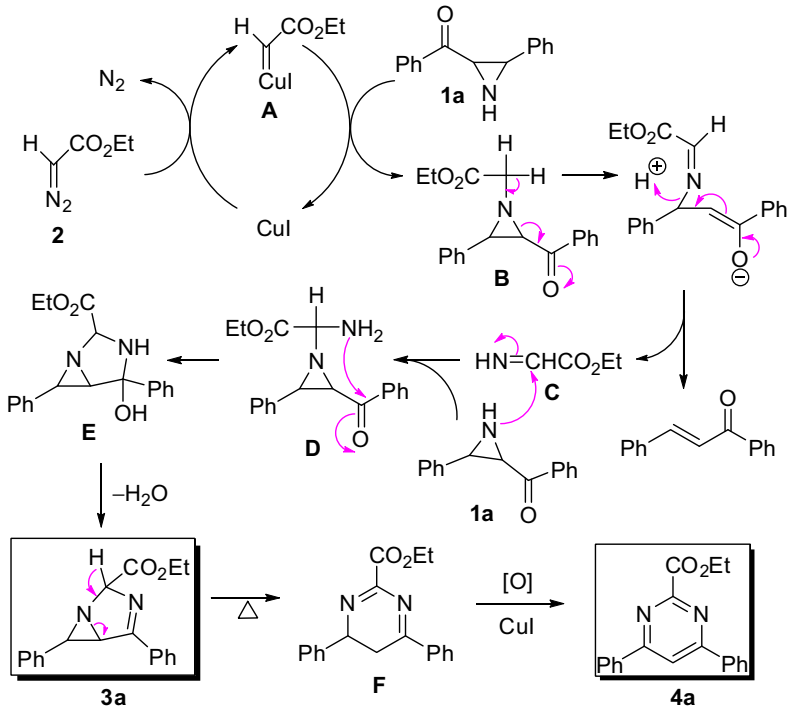
Table 3
Formation of substituted pyrimidines[a]



Entry	R^1/R^2	Product	Yield[b] (%)
1	C_6H_5/C_6H_5 (**1a**)	**4a**	53
2	C_6H_5/4-$MeOC_6H_4$ (**1g**)	**4b**	68
3	C_6H_5/4-BrC_6H_5 (**1m**)	**4c**	42

[a] Reaction conditions: **1** (0.5 mmol), **2** (2.0 mmol), CuI (0.05 mmol), DCE (5 mL), 3 days.
[b] Isolated yield refers to aziridine **1**.

was found that the electron-rich substitution on the phenyl ring of R^1 (Table 2, entries 4–6) and R^2 (Table 2, entries 7 and 9) gave better yields than the electron-deficient substitution (Table 2, entries 1–3). 2-Phenyl-3-pivaloyl aziridine (**1l**) did not work for



Scheme 2. Possible mechanism for the cascade reaction.

this reaction (Table 2, entry 12). Structures of 1,3-diazabicyclo[3.1.0]-hex-3-enes **3a–k** were confirmed by ^{1}H and ^{13}C NMR spectroscopy, HRMS and comparative analysis of the X-ray structure of **3a** (Fig. 1).[14]

1,3-Diazabicyclo[3.1.0]hex-3-enes **3** were relatively unstable when they were exposed to UV light.[8] It might undergo rearrangement and subsequent oxidation in the presence of sodium methoxide and result in the formation of the more stable pyrimidine.[7] By raising the reaction temperature to 80 °C and prolonging the reaction time to 72 h, pyrimidine skeletons were also formed in our cases(Table 3).

A proposed mechanism for this cascade reaction is shown in Scheme 2. Firstly, copper-stabilized carbene complex **A** is generated in situ by the reaction of EDA and CuI. Insertion of **A** to N–H bond of **1a** leads to the formation of intermediate **B**.[15] The ring opening of active aziridine **B**, assisted by the electron-withdrawing nature of carbonyl, results in the formation of stable chalcone and imine **C**.[16] Sequentially nucleophilic addition of **1a** to imine **C** gives multi-functionalized intermediate **D**. After intramolecular addition of amino group to the carbonyl of **D**, followed by dehydration, the final 1,3-diazabicyclo[3.1.0]hex-3-ene skeleton **3a** was obtained. Further ring-expansion of **3a**, due to the strain of fused rings as well as the acidity of the proton adjacent to the ester group, generates the dihydropyrimidine **F**, which is aromatized to pyrimidine **4a** if a harsh reaction condition is employed.

In conclusion, a novel synthesis of 1,3-diazabicyclo[3.1.0]hex-3-enes was developed via a copper (I)-catalyzed reaction between aziridines and ethyl diazoacetate. A possible mechanism for this cascade reaction was proposed. This example proved aziridines as useful starting materials in the construction of more complicated heterocyclic compounds.

Acknowledgment

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2010.07.026.

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13. General procedure for the synthesis of 1,3-diazabicyclo[3.1.0]hex-3-enes **3**: To a solution of aziridine **1** (0.5 mmol), and the CuI (0.05 mmol) in DCE (5 mL), was added ethyl diazoacetate (**2**, 1 mmol). The reaction mixture was stirred under N_2 atmosphere at 25 °C for 24 h. The mixture was diluted with ethyl acetate (10 mL) and then washed with saturated NaCl solution (10 mL) and dried over anhydrous Na_2SO_4. The solvent was evaporated and the crude product was purified by silica gel column chromatography with hexane–EtOAc. Characterization data for the selected products: **3a:** White solid, mp 134–

136 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.97–7.95 (2H, m), 7.56–7.52 (1H, m), 7.50–7.45 (2H, m), 7.36–7.30 (5H, m), 5.70 (1H, d, J = 2.8 Hz), 4.38–4.27 (2H, m), 3.79 (1H, t, J = 2.4 Hz), 2.56 (1H, d, J = 2.4 Hz), 1.37(3H, t, J = 7.2 Hz) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ: 173.8, 168.7, 137.1, 131.9, 131.2,128.8, 128.7, 128.5, 127.9, 126.5, 94.9, 61.7, 56. 6, 47.9, 14.1 ppm; IR (KBr) 2985, 1747, 1603, 1454, 1194, 1054, 753, 692 cm^{-1}; MS (ESI): m/z 329 ([M+Na]$^+$); HRMS (ESI) m/z calcd for $C_{19}H_{18}N_2O_2$ + Na^+: 329.1260; found: 329.1249. **3b**: White solid, mp 138–140 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.94–7.92 (2H, m), 7.55–7.52 (1H, m), 7.48–7.44 (2H, m), 7.34–7.26 (4H, m), 6.00 (1H, s), 4.36–4.23 (2H, m), 3.68 (1H, t, J = 2.0 Hz), 3.04 (1H, s), 1.32 (3H, t, J = 7.2 Hz) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ: 173.3, 168.1, 135.9, 133.6, 132.0, 131.0, 128.8, 128.7, 128.6, 127.9, 93.5, 61.9, 56.7, 43.8, 14.2 ppm; IR (KBr): 2983, 1747, 1605, 1494, 1193, 1060, 797, 698 cm^{-1}; MS (ESI): m/z 363 ([M+Na]$^+$); HRMS (ESI) m/z calcd for $C_{19}H_{17}ClN_2O_2$ + Na^+: 363.0871; found: 363.0877.

14. CCDC 777087 contains the supplementary crystallographic data for compounds **3a**. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12, Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.
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