JOC The Journal of Organic Chemistry

Note

pubs.acs.org/joc

Synthesis of α-Methylene-β-Lactams via PPh_3-Catalyzed Umpolung Cyclization of Propiolamides

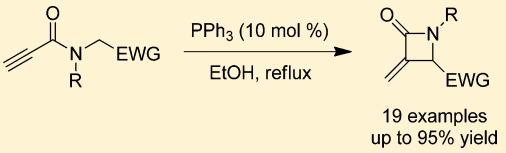
Lin Zhu,[†] Yan Xiong,[‡] and Chaozhong Li*[,†,‡]

[†]Department of Chemistry, University of Science and Technology of China, Hefei, Anhui 230026, P. R. China

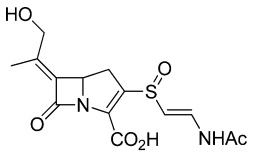
[‡]Shanghai Institute of Organic Chemistry, Chinese Academy of Sciences, 345 Lingling Road, Shanghai 200032, P. R. China

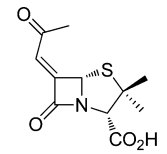
Supporting Information

ABSTRACT: We report herein a facile synthesis of α-methylene-β-lactams. Thus, under the catalysis of triphenylphosphine, a number of 2-propiolamidoacetates or α-propiolamido ketones in refluxing ethanol underwent umpolung cyclization to afford the corresponding 4-substituted 3-methyleneazetidin-2-ones in high yields.



β-Lactams are an intensively studied family of heterocycles primarily because of their biological activity.[1] For example, β-lactam antibiotics such as penicillins and cephalosporins have occupied a central role in the fight against pathogenic bacteria. α-Methylene-β-lactams (**1**) are important structural motifs widely embedded in β-lactam antibiotics such as β-lactamase inhibitors asparenomycin A and 6-(acetylmethylene)penicillanic acid.[2] In the meantime, they are also versatile synthetic intermediates owing to the unique combination of a four-membered ring and an α,β-unsaturated amide moiety. A number of methods have thus been developed for their synthesis,[3,4] including β-elimination of 3-substituted azetidin-2-ones, [2 + 2] cycloaddition of allenes with isocyanates, transition-metal-catalyzed carbonylation of 2-haloallylamines or 2-methyleneaziridines, and palladium-catalyzed direct oxidative carbonylation of *N*-allylamines very recently reported by Lei et al.[4n] However, these methods suffer from either limited scope of application or harsh experimental conditions. Therefore, the development of simple, economic, efficient, and general methods is certainly highly desirable. As our continuous interest in the construction of four-membered rings,[5] we report herein the facile synthesis of α-methylene-β-lactams via phosphine-catalyzed cyclization of propiolamides.


asparenomycin A


6-(acetylmethylene)-penicillanic acid


1

Nucleophilic phosphine organocatalysis has been demonstrated to be a versatile tool in organic synthesis.[6,7] In particular, the zwitterionic species generated from the conjugated addition of tertiary phosphines to activated carbon−carbon multiple bonds serve as important intermediates in the synthesis of carbo- or heterocyclic compounds.[6f] We envisioned that this strategy might be applied into the synthesis of β-lactams from propiolamides such as ethyl 2-(*N*-benzylpropiolamido)acetate

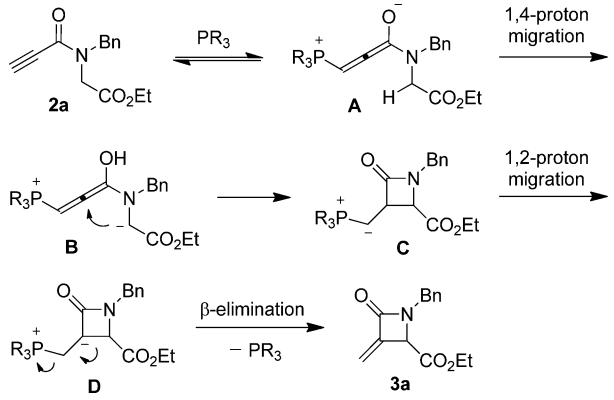


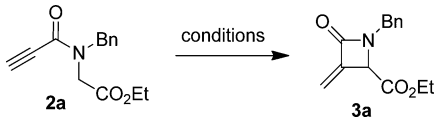
Figure 1. Proposed mechanism for the synthesis of β-lactam **3a**.

(**2a**). As proposed in Figure 1, the conjugated addition of a tertiary phosphine to **2a** should generate the zwitterionic intermediate **A**, which might undergo 1,4-proton migration to give α-ester anion **B**. The intermediate **B** might undergo intramolecular conjugated addition in a 4-*exo* mode to afford β-lactam intermediate **C**. The subsequent 1,2-proton migration (to give **D**), followed by β-elimination, might furnish α-methylene-β-lactam **3a** as the final product and regenerate the tertiary phosphine, which enters into the next catalytic circle. Nevertheless, the risk of this plan is obvious in that **2a** might undergo direct intramolecular conjugated addition in a 5-*endo* mode to produce the corresponding γ-lactam.

We then used amide **2a** as the model substrate to explore the above possibility. After the screening of a few typical experimental conditions (Table 1),[8] we were delighted to find that, with the catalysis of PPh_3 (10 mol %), the reaction of **2a** in refluxing ethanol for 12 h afforded the expected α-methylene-β-lactam **3a** in 70% isolated yield (entry 4, Table 1). No corresponding γ-lactam could be detected. To the best of our knowledge, this is the first example of four-membered ring

Received: October 3, 2014
Published: November 20, 2014

Table 1. Optimization of Reaction Conditions



entry[a]	catalyst (mol %)	additive (mol %)	solvent/temp	yield (%)[b]
1	PPh_3 (50)	AcOH (50)/AcONa (50)	PhMe, 100 °C	24
2	PPh_3 (50)	PhOH (100)	PhMe, 100 °C	21
3	PPh_3 (20)	EtOH (100)	PhMe, 100 °C	trace
4	PPh_3 (10)	none	EtOH, 80 °C	70
5	PPh_3 (10)	none	EtOH, rt	26
6	PBu_3 (10)	none	EtOH, 80 °C	trace

[a]Conditions: **2a** (0.2 mmol), solvent (8 mL), 12 h. [b]Isolated yield based on **2a**.

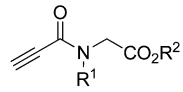
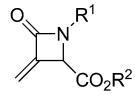
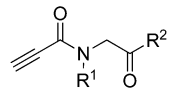
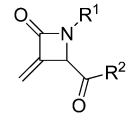
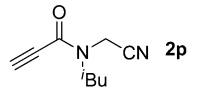
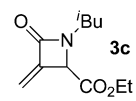
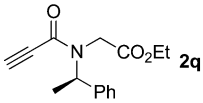
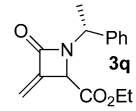
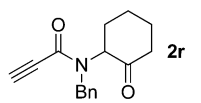
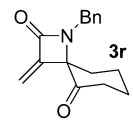
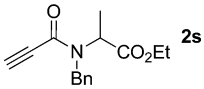
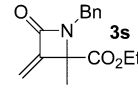
synthesis via nucleophilic phosphine organocatalysis. The cyclization also proceeded at rt, but in a much slower rate with a large portion (>50%) of **2a** recovered. However, when the catalyst PPh_3 was switched to PBu_3, only a trace amount of **3a** could be detected, while the conjugated addition of ethanol to **2a** prevailed to give the corresponding enol ether (entry 6, Table 1).[9]

A number of propiolamides were then subjected to the above optimized conditions (entry 4, Table 1), and the results are summarized in Table 2. In all cases, only the expected *β*-lactams were achieved, while no *γ*-lactams could be detected. Esters **2b**–**2h** with an *N*-alkyl or *N*-aryl substituent, which were readily prepared from the condensation of propiolic acid with glycine derivatives, underwent cyclization smoothly to give the corresponding lactams **3b**–**3h** in good to excellent yields. In particular, ester **2d** with a bulky *N*-*tert*-butyl group afforded *β*-lactam **3d** in almost quantitative yield. On the other hand, the analogous NH amide failed to give any cyclized product (not shown). These N-substituent effects should be attributed to the preferred *Z*-conformations of amide bonds. While the cyclization of **2d** requires the *Z*-conformation, which is also the predominant conformation for **2d**, the cyclization of the analogous NH amide requires the much unfavorable *E*-conformation. Other than *α*-amino esters, *α*-amino ketones are also excellent substrates for the synthesis of *β*-lactams. *α*-Methylene-*β*-lactams **3i**–**3o** were thus obtained in high yields from the corresponding *α*-amino ketones **2i**–**2o**. With *α*-amino nitrile **2p** as the substrate, the cyclization also proceeded smoothly. Nevertheless, the cyano group was further converted to the ethyl ester group under the experimental conditions. The optically pure substrate **2q** derived from (*R*)-1-phenylethanamine was also tested. The product **3q** was achieved in 86% yield. However, no diastereoselectivity was observed. The above reactions gave 4-monosubstituted 3-methyleneazetidin-2-ones. To explore the synthesis of 4,4-disubstituted derivatives, propiolamides **2r** and **2s** were prepared and subjected to the optimized reaction conditions. Indeed, the expected products **3r** and **3s** were obtained, albeit in lower yields. The decreased yields might be rationalized by the increased steric hindrance in the 4-*exo* cyclization step (from **B** to **C**). In addition, the cyclization now requires the unfavorable *E*-conformations.

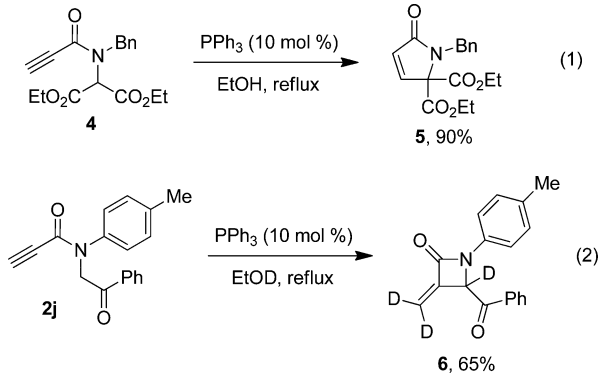
To further examine the scope and limitation of the above method, malonate **4** was prepared and tested under the optimized conditions (eq 1). Surprisingly, *γ*-lactam **5** was obtained in 90% yield, while no *β*-lactam could be detected, presumably because the malonate was more reactive than PPh_3 toward the activated C–C triple bond.

To provide more evidence on the proposed mechanism, we carried out the reaction of **2j** in EtOD (eq 2). Interestingly, trideuterated product **6** was obtained. This result suggests that the intermediates **A**–**D** have relatively long lifetimes to allow the H/D exchange, which, in turn, supports our proposed mechanism.

Table 2. Synthesis of *α*-Methylene-*β*-lactams

entry	substrate	product	time (h)	yield (%)
				
1	**2a** (R^1 = Bn, R^2 = Et)	**3a**	12	70
2	**2b** (R^1 = Ph, R^2 = Et)	**3b**	20	47
3	**2c** (R^1 = *i*-Bu, R^2 = Et)	**3c**	8	82
4	**2d** (R^1 = *t*-Bu, R^2 = Et)	**3d**	8	95
5	**2e** (R^1 = 4-Me-$C_6H_4CH_2$, R^2 = Et)	**3e**	18	72
6	**2f** (R^1 = 4-MeO-$C_6H_4CH_2$, R^2 = Et)	**3f**	18	66
7	**2g** (R^1 = 4-CF_3-$C_6H_4CH_2$, R^2 = Et)	**3g**	12	75
8	**2h** (R^1 = Bn, R^2 = *t*-Bu)	**3h**	12	70
				
9	**2i** (R^1 = R^2 = Ph)	**3i**	12	92
10	**2j** (R^1 = 4-Me-C_6H_4, R^2 = Ph)	**3j**	12	80
11	**2k** (R^1 = 4-Cl-C_6H_4, R^2 = Ph)	**3k**	12	77
12	**2l** (R^1 = 4-MeO-C_6H_4, R^2 = Ph)	**3l**	8	82
13	**2m** (R^1 = R^2 = 4-Cl-C_6H_4)	**3m**	12	78
14	**2n** (R^1 = 4-Cl-C_6H_4, R^2 = 4-MeO-C_6H_4)	**3n**	12	82
15	**2o** (R^1 = 4-Cl-C_6H_4, R^2 = Me)	**3o**	12	81
16	 **2p**	 **3c**	12	70
17	 **2q**	 **3q**	12	86
18	 **2r**	 **3r**	20	38
19	 **2s**	 **3s**	24	35

dx.doi.org/10.1021/jo502265a | J. Org. Chem. 2015, 80, 628–633



In conclusion, we have successfully developed a new protocol for the synthesis of α-methylene-β-lactams via triphenylphosphine-catalyzed umpolung cyclization of propiolamides under mild and metal-free conditions. The ready availability of propriolamides and easy operation of this transformation should encourage its further application in organic synthesis.

EXPERIMENTAL SECTION

General Information. Melting points were measured with a melting point instrument and were uncorrected. ^{1}H and ^{13}C NMR spectra were recorded using a 400 MHz NMR spectrometer. The chemical shifts are referenced to $CDCl_3$ (signals at 7.26 and 77.0 ppm, respectively) with TMS as the internal standard. IR spectra were obtained either as potassium bromide pellets or as liquid films between two potassium bromide pellets with a spectrometer. High-resolution mass spectrometry (HRMS) was performed on a TOF MS instrument with an ESI source.

Ethyl 2-(*N*-Benzylpropiolamido)acetate (2a). Typical Procedure. To a solution of propiolic acid (818 mg, 11 mmol) in CH_2Cl_2 (40 mL) was added DCC (2.35 g, 11 mmol) and DMAP (136 mg, 1.1 mmol) at −30 °C. The solution of ethyl 2-(benzylamino)acetate (1.93 g, 10 mmol) in CH_2Cl_2 (10 mL) was then added dropwise. The reaction mixture was stirred at rt for 24 h and then filtered by Celite. After removal of the solvent under reduced pressure, the crude product was purified by column chromatography on silica gel with hexane/ethyl acetate (5:1, v:v) as the eluent to give the pure **2a** as a colorless oil. Yield: 2.20 g (90%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.22−7.38 (m, 5H), 4.90/4.67 (2s, 2H), 4.19/3.99 (2s, 2H), 4.11−4.19 (m, 2H), 3.30/3.24 (2s, 1H), 1.21−1.26 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 168.5/168.1, 154.1/153.9, 135.4/135.2, 128.9/128.8, 128.6/128.3, 128.0/127.8, 80.2/79.9, 75.4/75.2, 61.6/61.4, 53.3/49.4, 48.7/45.2, 14.1; IR (neat): ν (cm^{-1}) 3241, 2983, 2938, 2106, 1746, 1642, 1431, 1199, 1026, 737, 699; ESI-MS: (m/z) 268.1 (M^+ + Na); HRMS calcd for $C_{14}H_{16}NO_3$ (M + H): 246.1125, found 246.1122.

Ethyl 2-(*N*-Phenylpropiolamido)acetate (2b). Yellow solid (1.80 g, 78%): mp 69−71 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.28−7.42 (m, 5H), 4.65/4.42 (2s, 2H), 4.16−4.27 (m, 2H), 3.30/2.89 (2s, 1H), 1.26 (t, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 168.6/168.0, 153.5/153.2, 141.5/140.3, 129.3, 128.7, 128.1, 80.5/80.2, 75.8, 61.8/61.5, 50.6, 14.1; IR (KBr): ν (cm^{-1}) 3246, 2984, 2940, 2106, 1746, 1643, 1594, 1381, 1201, 1020, 749, 697; ESI-MS: (m/z) 254.1 (M^+ + Na); HRMS calcd for $C_{13}H_{14}NO_3$ (M + H): 232.0968, found 232.0972.

Ethyl 2-(*N*-Isobutylpropiolamido)acetate (2c). Yellow oil (1.80 g, 85%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 4.30/4.08 (2s, 2H), 4.16−4.27 (m, 2H), 3.47/3.27 (2d, J = 7.6/6.0 Hz, 2H), 3.26/3.21 (2s, 1H), 1.88−1.96 (m, 1H), 1.26−1.323 (m, 3H), 0.97/0.91 (2d, J = 6.8 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 168.7/168.1, 154.2/154.1, 79.8/79.2, 75.6/75.5, 61.6/61.3, 57.3/53.3, 51.0/46.8, 27.4/26.7, 20.0/19.8, 14.1/14.0; IR (neat): ν (cm^{-1}) 3230, 2963, 2105, 1749, 1635, 1462, 1432, 1200, 1141, 1024; ESI-MS: (m/z) 234.1 (M^+ + Na); HRMS calcd for $C_{11}H_{17}NNaO_3$ (M + Na): 234.1101, found 234.1097.

Ethyl 2-(*N*-(*tert*-Butyl)propiolamido)acetate (2d). Colorless oil (1.50 g, 71%). ^{1}H NMR (400 MHz, $CDCl_3$): 4.41 (br s, 2H), 4.23 (q, J = 6.8 Hz, 2H), 3.30/2.99 (2s, 1H), 1.60/1.43 (2s, 9H), 1.29 (t, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) (predominant rotamer): δ 170.0, 154.4, 77.24, 77.16, 61.6, 58.2, 49.1, 28.1, 14.1; IR (neat): ν (cm^{-1}) 2981, 2342, 2100, 1751, 1648, 1593, 1383, 1195; ESI-MS: (m/z) 234.1 (M^+ + Na); HRMS calcd for $C_{11}H_{17}NNaO_3$ (M + Na): 234.1101, found 234.1104.

Ethyl 2-(*N*-(4-Methylbenzyl)propiolamido)acetate (2e). Yellow oil (2.23 g, 86%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.15/7.12 (2s, 2H), 4.85/4.62 (2s, 2H), 3.97−4.17 (m, 4H), 3.33/3.26 (2s, 1H), 2.33/2.31 (2s, 3H), 1.20−1.26 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 168.5/168.1, 154.1/153.8, 138.0/137.7, 132.4/132.2, 129.6/129.4, 128.6/127.9, 80.3/79.9, 75.4/75.3, 61.6/61.3, 53.0/49.2, 48.3/45.0, 21.1, 14.1; IR (neat): ν (cm^{-1}) 3243, 2981, 2935, 2105, 1745, 1640, 1432, 1197, 1023, 755; ESI-MS: (m/z) 282.1 (M^+ + Na); HRMS calcd for $C_{15}H_{18}NO_3$ (M + H): 260.1281, found 260.1279.

Ethyl 2-(*N*-(4-Methoxybenzyl)propiolamido)acetate (2f). Yellow oil (2.42 g, 88%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.15−7.21 (m, 2H), 6.84−6.90 (m, 2H), 4.84/4.61 (2s, 2H), 3.98−4.19 (m, 4H), 3.80/3.78 (2s, 3H), 3.33/3.24 (2s, 1H), 1.21−1.27 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 168.5/168.1, 159.6/159.4, 154.0/153.7, 130.0/129.3, 127.3/127.1, 114.3/114.2, 80.2/79.7, 75.4/75.3, 61.6/61.3, 55.3/55.2, 52.7/40.1, 48.0/44.9, 14.1; IR (neat): ν (cm^{-1}) 3245, 2980, 2937, 2105, 1745, 1638, 1612, 1513, 1437, 1249, 1198, 1028; ESI-MS: (m/z) 298.1 (M^+ + Na); HRMS calcd for $C_{15}H_{18}NO_4$ (M + H): 276.1230, found 276.1232.

Ethyl 2-(*N*-(4-(Trifluoromethyl)benzyl)propiolamido)acetate (2g). Yellow oil (2.57 g, 82%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.64/7.60 (2d, J = 8.0 Hz, 2H), 7.43/7.39 (2d, J = 8.0 Hz, 2H), 4.99/4.75 (2s, 2H), 4.24/4.02 (2s, 2H), 4.14−4.24 (m, 2H), 3.30/3.25 (2s, 1H), 1.22−1.27 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 168.3/167.9, 154.3/154.0, 139.7/139.5, 130.4 (q, J = 32.8 Hz), 128.7/128.0, 125.9/125.7 (2q, J = 4.4 Hz), 124.0/123.9 (2q, J = 270.5 Hz), 80.4/80.2, 75.1/74.9, 61.8/61.5, 52.9/49.7, 48.5/45.5, 14.0; IR (neat): ν (cm^{-1}) 3242, 2986, 2940, 2107, 1746, 1642, 1416, 1326, 1201, 1166, 1124, 1067; ESI-MS: (m/z) 336.1 (M^+ + Na); HRMS calcd for $C_{15}H_{15}NO_3F_3$ (M + H): 314.0999, found 314.0998.

***tert*-Butyl 2-(*N*-Benzylpropiolamido)acetate (2h).** White solid (2.43 g, 89%): mp 71−73 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.23−7.37 (m, 5H), 4.89/4.67 (2s, 2H), 4.07/3.91 (2s, 2H), 3.20/3.14 (2s, 1H), 1.44/1.43 (2s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 167.5/167.2, 154.2/153.9, 135.6/135.4, 128.9/128.8, 128.7/128.0, 128.2/127.8, 82.6/82.2, 79.8/79.2, 75.5/75.4, 53.3/50.2, 48.8/45.8, 28.0; IR (KBr): ν (cm^{-1}) 3238, 2980, 2935, 2105, 1741, 1643, 1431, 1369, 1221, 1155, 748, 699; ESI-MS: (m/z) 296.1 (M^+ + Na); HRMS calcd for $C_{16}H_{20}NO_3$ (M + H): 274.1438, found 274.1443.

***N*-(2-Oxo-2-phenylethyl)-*N*-phenylpropiolamide (2i).** White solid (2.03 g, 77%): mp 84−86 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.94 (d, J = 7.6 Hz, 2H), 7.36−7.59 (m, 8H), 5.36/5.18 (2s, 2H), 3.04/2.87 (2s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) (predominant rotamer): δ 192.3, 153.3, 141.8, 134.8, 133.8, 129.3, 128.9, 128.6, 128.3, 128.0, 80.5, 76.0, 55.7; IR (KBr): ν (cm^{-1}) 2106, 1695, 1647, 1593, 1493, 1409, 1387, 1230, 759, 699, 688; ESI-MS: (m/z) 286.1 (M^+ + Na); HRMS calcd for $C_{17}H_{13}NNaO_2$ (M + Na): 286.0838, found 286.0842.

***N*-(2-Oxo-2-phenylethyl)-*N*-(*p*-tolyl)propiolamide (2j).** White solid (2.08 g, 75%): mp 120−122 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.91−7.96 (m, 2H), 7.56−7.62 (m, 1H), 7.44−7.52 (m, 2H), 7.34 (d, J = 8.4 Hz, 2H), 7.18−7.23 (m, 2H), 5.34/5.15 (2s, 2H), 3.03/2.87 (2s, 1H), 2.36/2.32 (2s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) (predominant rotamer): δ 192.3, 153.4, 139.2, 138.6, 134.9, 133.8, 129.9, 128.8, 128.1, 128.0, 80.3, 76.1, 55.8, 21.2; IR (KBr): ν (cm^{-1}) 2103, 1697, 1687, 1635, 1510, 1418, 1390, 1221, 981, 757, 738, 686, 599; ESI-MS: (m/z) 300.1 (M^+ + Na); Anal. Calcd for $C_{18}H_{15}NO_2$: C, 77.96; H, 5.45; N, 5.05; Found: C, 77.91; H, 5.42; N, 5.11.

***N*-(4-Chlorophenyl)-*N*-(2-oxo-2-phenylethyl)propiolamide (2k).** White solid (2.26 g, 76%): mp 147−149 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.89−7.95 (m, 2H), 7.29−7.59 (m, 7H), 5.34/5.13 (2s, 2H), 3.06/2.91 (2s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) (predominant rotamer): δ 192.0, 153.1, 140.2, 134.6, 134.4, 133.9,

dx.doi.org/10.1021/jo502265a | J. Org. Chem. 2015, 80, 628−633

129.8, 129.5, 128.8, 127.9, 80.8, 75.7, 55.5; IR (KBr): ν (cm^{-1}) 2102, 1692, 1651, 1492, 1417, 1321, 1225, 1012; ESI-MS: (m/z) 320.0 (M^+ + Na); HRMS calcd for $C_{17}H_{12}ClNNaO_2$ (M + Na): 320.0449, found 320.0461.

***N*-(4-Methoxyphenyl)-*N*-(2-oxo-2-phenylethyl)propiolamide (2l).** White solid (2.14 g, 73%): mp 125−127 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.89−7.95 (m, 2H), 7.25−7.59 (m, 5H), 6.76−6.89 (m, 2H), 5.35/5.13 (2s, 2H), 3.78/3.73 (2s, 3H), 3.09/2.92 (2s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) (predominant rotamer): δ 192.4, 159.5, 153.6, 134.9, 134.5, 133.8, 129.6, 128.8, 128.0, 114.4, 80.5, 76.1, 55.9, 54.5; IR (KBr): ν (cm^{-1}) 2931, 2106, 1700, 1641, 1511, 1221, 1031, 839, 754, 737, 690; ESI-MS: (m/z) 316.1 (M^+ + Na); HRMS calcd for $C_{18}H_{15}NNaO_3$ (M + Na): 316.0944, found 316.0938.

***N*-(4-Chlorophenyl)-*N*-(2-(4-chlorophenyl)-2-oxoethyl)-propiolamide (2m).** White solid (2.39 g, 72%): mp 126−128 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.85−7.91 (m, 2H), 7.29−7.49 (m, 6H), 5.29/5.09 (2s, 2H), 3.01/2.91 (2s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) (predominant rotamer): δ 191.1, 153.1, 140.4, 140.1, 134.6, 133.0, 129.8, 129.6, 129.4, 129.2, 80.9, 75.6, 55.4; IR (KBr): ν (cm^{-1}) 2109, 1704, 1641, 1590, 1489, 1381, 1315, 1220, 1090, 983, 819; ESI-MS: (m/z) 354.0 (M^+ + Na); HRMS calcd for $C_{17}H_{11}Cl_2NNaO_2$ (M + Na): 354.0059, found 354.0067.

***N*-(4-Chlorophenyl)-*N*-(2-(4-methoxyphenyl)-2-oxoethyl)-propiolamide (2n).** White solid (2.39 g, 73%): mp 90−92 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.83−7.91 (m, 2H), 7.37 (d, J = 7.2 Hz, 2H), 7.30 (d, J = 8.4 Hz, 2H), 6.86−6.92 (m, 2H), 5.28/5.07 (2s, 2H), 3.81/3.79 (2s, 3H), 3.08/2.92 (2s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 191.4/190.6, 164.3/164.1, 154.0/153.1, 140.4/139.3, 134.3/133.1, 130.3, 129.8, 129.4/129.3, 128.2/127.7, 114.3/114.1, 80.8/79.9, 75.9, 58.1/55.6, 55.2; IR (KBr): ν (cm^{-1}) 2111, 1686, 1648, 1602, 1492, 1237, 1176, 1011, 977; ESI-MS: (m/z) 350.1 (M^+ + Na); HRMS calcd for $C_{18}H_{14}ClNNaO_3$ (M + Na): 350.0554, found 350.0560.

***N*-(4-Chlorophenyl)-*N*-(2-oxopropyl)propiolamide (2o).** White solid (1.93 g, 82%): mp 110−112 °C. ^{1}H NMR 400 MHz, $CDCl_3$): δ 7.22−7.39 (m, 4H), 4.70/4.48 (2s, 2H), 3.18/2.89 (2s, 1H), 2.120/2.16 (2s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) (predominant rotamer): δ 200.7, 152.9, 140.1, 134.5, 129.6, 129.5, 80.8, 75.5, 58.5, 27.1; IR (KBr): ν (cm^{-1}) 3238, 2108, 1736, 1635, 1493, 1427, 1383, 1319, 1176, 753, 721; ESI-MS: (m/z) 236.1 (M^++H); HRMS calcd for $C_{12}H_{11}ClNO_2$ (M + H): 236.0473, found 236.0471.

***N*-(Cyanomethyl)-*N*-isobutylpropiolamide (2p).** Yellow oil (1.38 g, 84%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 4.48/4.23 (2s, 2H), 3.26−3.46 (m, 3H), 1.91−2.00 (m, 1H), 0.90/0.85 (2d, J = 6.8 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 153.7/153.2, 114.7/114.9, 81.2/81.5, 74.7/74.5, 56.9/52.7, 33.0/37.8, 27.1/26.5, 19.8/19.6; IR (neat): ν (cm^{-1}) 3247, 2965, 2109, 1637, 1430, 1255, 1145, 742; ESI-MS: (m/z) 187.1 (M^+ + Na); HRMS calcd for $C_9H_{12}N_2NaO$ (M + Na): 187.0842, found 187.0847.

***(R)*-Ethyl 2-(*N*-(1-Phenylethyl)propiolamido)acetate (2q).** Yellow oil (2.10 g, 81%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.29−7.39 (m, 5H), 5.99/5.85 (2q, J = 7.2 Hz, 1H), 3.97−4.16 (m, 3H), 3.83/3.53 (2d, J = 16.8 Hz, 1H), 3.23/3.07 (2s, 1H), 1.65/1.51 (2d, J = 7.2 Hz, 3H), 1.20 (t, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 168.9/168.1, 154.3/153.5, 138.8/138.7, 128.7/128.6, 128.1/128.0, 127.7/127.1, 79.9/78.9, 75.8/75.4, 61.5/61.2, 56.8/51.2, 46.3/43.2, 17.3/15.9, 14.0; IR (neat): ν (cm^{-1}) 3244, 2980, 2105, 1749, 1636, 1541, 1457, 1200, 1027; ESI-MS: (m/z) 282.1 (M^+ + Na); HRMS calcd for $C_{15}H_{18}NO_3$ (M + H): 260.1281, found 260.1279.

***N*-Benzyl-*N*-(2-oxocyclohexyl)propiolamide (2r).** Yellow oil (1.79 g, 70%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.18−7.35 (m, 5H), 5.20/5.13 (2d, J = 16.4 Hz, 1H), 4.92/4.68 (2dd, J = 12.0, 6.0 Hz, 1H), 4.54/4.02 (2d, J = 16.4 Hz, 1H), 3.26/3.11 (2s, 1H), 2.45−2.58 (m, 1H), 2.26−2.42 (m, 1H), 1.57−1.98 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 205.5/204.5, 154.7/154.5, 137.8/137.5, 128.7/128.5, 127.6/127.1, 127.0/126.8, 80.2/79.4, 76.0/75.9, 67.5/63.2, 51.9/47.6, 41.3/41.2, 32.9/31.2, 26.2/25.9, 24.8/24.6; IR (neat): ν (cm^{-1}) 2935, 2103, 1720, 1631, 1414, 1123, 1021; ESI-MS: (m/z) 278.1 (M^+ + Na); HRMS calcd for $C_{16}H_{17}NNaO_2$ (M + Na): 278.1152, found 278.1159.

Ethyl 2-(*N*-Benzylpropiolamido)propanoate (2s). Yellow oil (1.84 g, 71%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.21−7.38 (m, 5H), 5.08/4.42 (2q, J = 7.2 Hz, 1H), 4.97/4.81 (2d, J = 16.4 Hz, 1H), 4.78/4.45 (2d, J = 16.0 Hz, 1H), 3.90−4.13 (m, 2H), 3.23/3.14 (2s, 1H), 1.43/1.31 (2d, J = 7.2 Hz, 3H), 1.16−1.22 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 170.8/170.5, 154.5/153.8, 137.1/136.4, 128.7/128.4, 127.9/127.4, 127.8/127.6, 80.1/79.3, 75.9/75.6, 61.7/61.3, 57.0/53.8, 52.4/46.6, 16.1/14.5, 14.0; IR (neat): ν (cm^{-1}) 3245, 2986, 2105, 1739, 1638, 1429, 1221, 1112, 730, 698; ESI-MS: (m/z) 282.1 (M^+ + Na); HRMS calcd for $C_{15}H_{18}NO_3$ (M + H): 260.1281, found 260.1280.

Diethyl 2-(*N*-Benzylpropiolamido)malonate (4).[10] Yellow oil (2.32 g, 73%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.18−7.35 (m, 5H), 5.65/5.15 (2s, 1H), 4.98/4.81 (2s, 2H), 4.02−4.10 (m, 2H), 3.87−3.96 (m, 2H), 3.37/3.31 (2s, 1H), 1.14 (t, J = 6.8 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 165.4/165.1, 154.5/154.3, 136.1/135.4, 128.5/128.2, 127.9/127.4, 127.8/127.6, 81.3/81.1, 75.0/74.7, 63.9/62.5, 62.2/60.0, 52.4/48.0, 13.7.

Ethyl 1-Benzyl-3-methylene-4-oxoazetidine-2-carboxylate (3a). Typical Procedure. To the solution of **2a** (49 mg, 0.2 mmol) in absolute EtOH (8 mL) was added PPh_3 (5.2 mg, 0.02 mmol). The solution was stirred at reflux for 12 h. The resulting mixture was then cooled down to rt and concentrated in vacuo. The residue was purified by column chromatography on silica gel with hexane/EtOAc (10:1, v:v) as the eluent to get the pure product **3a** as a colorless oil. Yield: 35 mg (70%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.17−7.29 (m, 5H), 5.70 (t, J = 1.6 Hz, 1H), 5.25 (t, J = 1.6 Hz, 1H), 4.88 (d, J = 14.8 Hz, 1H), 4.28 (s, 1H), 4.24 (d, J = 15.2 Hz, 1H), 4.06−4.20 (m, 2H), 1.19 (t, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 168.6, 162.5, 144.9, 134.8, 128.9, 128.5, 128.0, 110.6, 61.7, 58.8, 45.4, 14.1; IR (neat): ν (cm^{-1}) 1764, 1496, 1455, 1383, 1203, 1107, 1028, 928, 702; ESI-MS: (m/z) 268.1 (M^+ + Na); HRMS calcd for $C_{14}H_{15}NNaO_3$ (M + Na): 268.0944, found 268.0944.

Ethyl 3-Methylene-4-oxo-1-phenylazetidine-2-carboxylate (3b). Yellow solid (22 mg, 47%): mp 70−72 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.32−7.37 (m, 4m), 7.10−7.15 (m, 1H), 5.92 (t, J = 2.0 Hz, 1H), 5.48 (t, J = 2.0 Hz, 1H), 4.95 (t, J = 1.6 Hz, 1H), 4.20−4.34 (m, 2H), 1.25 (t, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 168.0, 159.4, 143.7, 137.3, 129.3, 124.7, 116.7, 111.9, 62.1, 59.8, 14.1; IR (KBr): ν (cm^{-1}) 1753, 1598, 1502, 1369, 1198, 1122, 1023, 754; ESI-MS: (m/z) 254.1 (M^+ + Na); HRMS calcd for $C_{13}H_{14}NO_3$ (M + H): 232.0968, found 232.0974.

Ethyl 1-Isobutyl-3-methylene-4-oxoazetidine-2-carboxylate (3c). Colorless oil (35 mg, 82%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 5.71 (t, J = 1.6 Hz, 1H), 5.28 (t, J = 1.2 Hz, 1H), 4.53 (s, 1H), 4.16−4.29 (m, 2H), 3.36 (dd, J = 14.0, 8.4 Hz, 1H), 3.07 (1H, dd, J = 14.0, 6.4 Hz, 1H), 1.86−1.94 (m, 1H), 1.28 (t, J = 7.2 Hz, 3H), 0.94 (d, J = 6.8 Hz, 3H), 0.90 (d, J = 6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 168.8, 163.0, 145.1, 109.9, 61.7, 60.3, 49.2, 27.5, 20.4, 20.3, 14.1; IR (neat): ν (cm^{-1}) 2961, 2934, 2873, 1763, 1467, 1387, 1295, 1198, 1078, 1028; ESI-MS: (m/z) 234.2 (M^+ + Na); HRMS calcd for $C_{11}H_{17}NNaO_3$ (M + Na): 234.1101, found 234.1101.

Ethyl 1-(*tert*-Butyl)-3-methylene-4-oxoazetidine-2-carboxylate (3d). Colorless oil (40 mg, 95%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 5.66 (t, J = 1.6 Hz, 1H), 5.18 (t, J = 1.6 Hz, 1H), 4.53 (s, 1H), 4.15−4.29 (m, 2H), 1.36 (s, 9H), 1.27 (t, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 169.9, 161.9, 144.5, 108.9, 61.7, 59.0, 54.4, 27.8, 14.1; IR (neat): ν (cm^{-1}) 2980, 1754, 1463, 1370, 1354, 1313, 1189, 1111, 1033, 929; ESI-MS: (m/z) 234.1 (M^+ + Na); HRMS calcd for $C_{11}H_{17}NNaO_3$ (M + Na): 234.1101, found 234.1103.

Ethyl 1-(4-Methylbenzyl)-3-methylene-4-oxoazetidine-2-carboxylate (3e). Colorless oil (37 mg, 72%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.11−7.16 (m, 4H), 5.75 (t, J = 1.6 Hz, 1H), 5.30 (s, 1H), 4.91 (d, J = 14.8 Hz, 1H), 4.32 (s, 1H), 4.14−4.27 (m, 3H), 2.32 (s, 3H), 1.26 (t, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 168.7, 162.5, 144.9, 137.8, 131.7, 129.6, 128.5, 110.5, 61.7, 58.7, 45.1, 21.1, 14.1; IR (neat): ν (cm^{-1}) 1766, 1516, 1382, 1203, 1101, 1027, 924,

dx.doi.org/10.1021/jo502265a | J. Org. Chem. 2015, 80, 628−633

795; ESI-MS: (m/z) 282.1 (M^+ + Na); HRMS calcd for $C_{15}H_{17}NNaO_3$ (M + Na): 282.1101, found 282.1100.

Ethyl 1-(4-Methoxybenzyl)-3-methylene-4-oxoazetidine-2-carboxylate (3f). Colorless oil (36 mg, 66%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.16 (d, J = 8.0 Hz, 2H), 6.85 (d, J = 8.8 Hz, 2H), 5.74 (t, J = 1.6 Hz, 1H), 5.29 (t, J = 1.6 Hz, 1H), 4.88 (d, J = 14.8 Hz, 1H), 4.31 (s, 1H), 4.16−4.25 (m, 3H), 3.78 (s, 3H), 1.26 (t, J = 6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 168.7, 162.4, 159.4, 144.8, 129.9, 126.8, 114.3, 110.4, 61.7, 58.6, 55.3, 44.8, 14.1; IR (neat): ν (cm^{-1}) 2982, 1763, 1612, 1514, 1443, 1382, 1247, 1100, 1030, 924, 820; ESI-MS: (m/z) 298.0 (M^+ + Na); HRMS calcd for $C_{15}H_{17}NNaO_4$ (M + Na): 298.1050, found 298.1050.

Ethyl 3-Methylene-4-oxo-1-(4-(trifluoromethyl)benzyl)-azetidine-2-carboxylate (3g). Colorless oil (47 mg, 75%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.57 (d, J = 8.0 Hz, 2H), 7.37 (d, J = 8.4 Hz, 2H), 5.77 (t, J = 1.6 Hz, 1H), 5.34 (t, J = 1.2 Hz, 1H), 4.92 (d, J = 15.6 Hz, 1H), 4.40 (d, J = 16.0 Hz, 1H), 4.38 (s, 1H), 4.10−4.24 (m, 2H), 1.22 (t, J = 6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 168.4, 162.5, 144.7, 139.2, 130.3 (q, J = 32.8 Hz), 128.7, 125.8 (q, J = 4.4 Hz), 123.9 (q, J = 270.5 Hz), 111.2, 61.8, 59.1, 45.0, 14.0; IR (neat): ν (cm^{-1}) 2983, 2361, 2340, 1767, 1620, 1384, 1326, 1121, 1066, 1020, 926; ESI-MS: (m/z) 336.0 (M^+ + Na); HRMS calcd for $C_{15}H_{14}F_3NNaO_3$ (M + Na): 336.0818, found 336.0810.

***tert*-Butyl 1-Benzyl-3-methylene-4-oxoazetidine-2-carboxylate (3h).** Yellow solid (38 mg, 70%): mp 73−75 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.24−7.37 (m, 5H), 5.75 (t, J = 2.0 Hz, 1H), 5.29 (br s, 1H), 4.94 (d, J = 14.8 Hz, 1H), 4.31 (d, J = 14.8 Hz, 1H), 4.25 (1H, s), 1.46 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 167.8, 162.6, 145.2, 134.9, 128.9, 128.5, 128.0, 110.1, 82.8, 59.4, 45.3, 28.0; IR (KBr): ν (cm^{-1}) 2979, 1768, 1740, 1370, 1152, 1108, 701; ESI-MS: (m/z) 296.1 (M^+ + Na); HRMS calcd for $C_{16}H_{19}NNaO_3$ (M + Na): 296.1257, found 296.1263.

4-Benzoyl-3-methylene-1-phenylazetidin-2-one (3i). White solid (48 mg, 92%): mp 193−195 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.07 (d, J = 7.6 Hz, 2H), 7.70 (t, J = 7.2 Hz, 1H), 7.58 (t, J = 7.6 Hz, 2H), 7.30−7.25 (m, 4H), 7.09−7.13 (m, 1H), 5.95 (s, 1H), 5.90 (d, J = 1.6 Hz, 1H), 5.26 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 191.3, 159.2, 144.0, 137.6, 134.6, 134.5, 129.3, 129.2, 128.7, 124.6, 117.1, 111.9, 64.1; IR (KBr): ν (cm^{-1}) 1764, 1682, 1596, 1505, 1494, 1377, 1229, 1116, 764, 750, 691. ESI-MS: (m/z) 286.0 (M^+ + Na); HRMS calcd for $C_{17}H_{13}NNaO_2$ (M + Na): 286.0838, found 286.0841.

4-Benzoyl-3-methylene-1-(*p*-tolyl)azetidin-2-one (3j). White solid (44 mg, 80%): mp 120−122 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.06 (d, J = 7.6 Hz, 2H), 7.69 (t, J = 7.6 Hz, 1H), 7.58 (t, J = 7.6 Hz, 2H), 7.24 (d, J = 8.4 Hz, 2H), 7.12 (d, J = 8.4 Hz, 2H), 5.91 (s, 1H), 5.88 (t, J = 2.0 Hz, 1H), 5.24 (d, J = 2.0 Hz, 1H), 2.31 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 191.5, 159.0, 144.1, 135.1, 134.7, 134.4, 134.3, 129.7, 129.2, 128.6, 117.0, 111.5, 64.1, 21.0; IR (KBr): ν (cm^{-1}) 1759, 1683, 1515, 1379, 1228, 1124, 932, 814, 699; ESI-MS: (m/z) 300.1 (M^+ + Na); HRMS calcd for $C_{18}H_{16}NO_2$ (M + H): 278.1176, found 278.1174.

4-Benzoyl-1-(4-chlorophenyl)-3-methyleneazetidin-2-one (3k). White solid (46 mg, 77%): mp 124−126 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.06 (d, J = 7.8 Hz, 2H), 7.71 (t, J = 7.2 Hz, 1H), 7.59 (t, J = 8.0 Hz, 2H), 7.29 (s, 4H), 5.92−5.94 (m, 2H), 5.28 (t, J = 2.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 191.0, 159.0, 143.8, 136.1, 134.7, 134.4, 129.6, 129.4, 129.3, 128.7, 118.3, 112.5, 64.2; IR (KBr): ν (cm^{-1}) 1746, 1691, 1595, 1494, 1383, 1128, 1089, 923, 826; ESI-MS: (m/z) 320.1 (M^+ + Na); HRMS calcd for $C_{17}H_{12}ClNNaO_2$ (M + Na): 320.0449, found 320.0456.

4-Benzoyl-1-(4-methoxyphenyl)-3-methyleneazetidin-2-one (3l). White solid (48 mg, 82%): mp 127−129 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.06 (d, J = 8.4 Hz, 2H), 7.69 (t, J = 7.6 Hz, 1H), 7.58 (t, J = 8.0 Hz, 2H), 7.30 (d, J = 8.8 Hz, 2H), 6.86 (d, J = 9.2 Hz, 2H), 5.90 (s, 1H), 5.87 (d, J = 2.4 Hz, 1H), 5.23 (t, J = 2.0 Hz, 1H), 3.78 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 191.7, 158.8, 156.6, 144.2, 134.6, 134.5, 131.2, 129.3, 128.6, 118.4, 114.5, 111.3, 64.2, 55.5; IR (KBr): ν (cm^{-1}) 1746, 1686, 1513, 1446, 1387, 1297, 1251, 1236, 828, 765; ESI-MS: (m/z) 316.0 (M^+ + Na); HRMS calcd for $C_{18}H_{15}NNaO_3$ (M + Na): 316.0944, found 316.0954.

4-(4-Chlorobenzoyl)-1-(4-chlorophenyl)-3-methyleneazetidin-2-one (3m). White solid (52 mg, 78%): mp 166−168 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.97 (d, J = 8.8 Hz, 2H), 7.54 (t, J = 8.8 Hz, 2H), 7.22−7.27 (m, 4H), 5.90 (t, J = 2.0 Hz, 1H), 5.83 (s, 1H), 5.23−5.24 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 190.0, 158.8, 143.5, 141.4, 135.9, 132.6, 129.9, 129.7, 129.6, 129.3, 118.2, 112.6, 64.1; IR (KBr): ν (cm^{-1}) 1747, 1690, 1587, 1493, 1378, 1322, 1228, 1125, 1092, 997, 827, 794; ESI-MS: (m/z) 354.1 (M^+ + Na); HRMS calcd for $C_{17}H_{11}Cl_2NNaO_2$ (M + Na): 354.0059, found 354.0063.

1-(4-Chlorophenyl)-4-(4-methoxybenzoyl)-3-methyleneazetidin-2-one (3n). White solid (54 mg, 82%): mp 170−172 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.03 (d, J = 8.4 Hz, 2H), 7.26 (d, J = 8.0 Hz, 4H), 7.04 (d, J = 9.2 Hz, 2H), 5.88−5.90 (m, 2H), 5.27 (dd, J = 0.8, 1.6 Hz, 1H), 3.91 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 189.3, 164.7, 159.1, 144.1, 136.1, 131.0, 129.4, 129.2, 127.3, 118.2, 114.5, 112.1, 64.0, 55.7; IR (KBr): ν (cm^{-1}) 2919, 1748, 1679, 1603, 1497, 1382, 1262, 1244, 1180, 1094, 834, 805; ESI-MS: (m/z) (M^+ + Na) 350.0; HRMS calcd for $C_{18}H_{14}ClNNaO_3$ (M + Na): 350.0554, found 350.0548.

4-Acetyl-1-(4-chlorophenyl)-3-methyleneazetidin-2-one (3o). White solid (38 mg, 81%): mp 182−184 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.30−7.33 (m, 2H), 7.23−7.26 (m, 2H), 5.98 (t, J = 1.6 Hz, 1H), 5.45 (dd, J = 1.2, 2.4 Hz, 1H), 4.84 (t, J = 1.6 Hz, 1H), 2.16 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 203.5, 159.3, 143.1, 135.8, 130.0, 129.6, 117.6, 113.3, 66.9, 24.9; IR (KBr): ν (cm^{-1}) 2923, 1741, 1720, 1497, 1387, 1172, 1093, 940, 826, 635; ESI-MS: (m/z) (M^+ + Na) 258.2; HRMS calcd for $C_{12}H_{10}ClNNaO_2$ (M + Na): 258.0292, found 258.0289.

Ethyl 3-Methylene-4-oxo-1-((*R*)-1-phenylethyl)azetidine-2-carboxylate (3q). This compound was obtained as a mixture of two inseparable stereoisomers in an ∼1:1 ratio (45 mg, 86%). Colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.23−7.32 (m, 5H), 5.69/5.67 (2t, J = 1.6 Hz, 1H), 5.21/5.18 (2t, J = 2.4 Hz, 1H), 5.07/4.73 (2q, J = 6.8/7.6 Hz, 1H), 4.30/3.23 (2t, J = 1.6 Hz, 1H), 4.03−4.18 (m, 2H), 1.78/1.63 (2d, J = 7.6/6.8 Hz, 3H), 1.20/1.15 (2t, J = 6.8/7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 169.1/168.8, 162.5, 144.5/144.4, 140.7/139.1, 128.8, 128.0/127.9, 127.2/126.8, 110.0, 61.7/61.6, 59.3/59.0, 55.6/52.4, 20.2/18.8, 14.0; IR (neat): ν (cm^{-1}) 2982, 2933, 1751, 1456, 1373, 1303, 1196, 1029, 927, 765, 702; ESI-MS: (m/z) (M^+ + Na) 282.0; HRMS calcd for $C_{15}H_{17}NNaO_3$ (M + Na): 282.1101, found 282.1099.

1-Benzyl-3-methylene-1-azaspiro[3.5]nonane-2,5-dione (3r). Yellow solid (19 mg, 38%): mp 101−103 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.25−7.33 (m, 5H), 5.74 (d, J = 2.4 Hz, 1H), 5.36 (d, J = 2.4 Hz, 1H), 5.02 (d, J = 15.2 Hz, 1H), 4.32 (d, J = 15.6 Hz, 1H), 2.58−2.63 (m, 1H), 2.44 (td, J = 14.4, 6.4 Hz, 1H), 2.06−2.12 (m, 1H), 1.52−1.88 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 205.6, 161.8, 151.1, 137.0, 128.6, 128.4, 127.7, 108.7, 75.0, 44.9, 41.3, 36.5, 25.9, 23.4; IR (KBr): ν (cm^{-1}) 2941, 1755, 1716, 1496, 1454, 1385, 1112, 791, 703; ESI-MS: (m/z) 278.2 (M^+ + Na); HRMS calcd for $C_{16}H_{17}NNaO_2$ (M + Na): 278.1152, found 278.1150.

Ethyl 1-Benzyl-2-methyl-3-methylene-4-oxoazetidine-2-carboxylate (3s). Colorless oil (18 mg, 35%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.26−7.33 (m, 5H), 5.68 (d, J = 2.0 Hz, 1H), 5.25 (d, J = 2.0 Hz, 1H), 4.78 (d, J = 15.2 Hz, 1H), 4.41 (d, J = 15.2 Hz, 1H), 4.12 (q, J = 7.2 Hz, 2H), 1.36 (s, 3H), 1.21 (t, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 170.9, 162.5, 150.9, 136.0, 128.8, 128.7, 127.8, 108.7, 67.6, 61.8, 44.7, 20.1, 14.0; IR (neat): ν (cm^{-1}) 1762, 1738, 1605, 1455, 1375, 1262, 1121, 1020, 927, 702; ESI-MS: (m/z) 282.1 (M^+ + Na); HRMS calcd for $C_{15}H_{17}NNaO_3$ (M + Na): 282.1101, found 282.1105.

Diethyl 1-Benzyl-5-oxo-1*H*-pyrrole-2,2(5*H*)-dicarboxylate (5).[10] Yellow oil (57 mg, 90%); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.19−7.27 (m, 5H), 7.13 (d, J = 6.0 Hz, 1H), 6.37 (d, J = 6.0 Hz, 1H), 4.88 (s, 2H), 3.94 (q, J = 7.2 Hz, 4H), 1.11 (t, J = 7.2 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 171.3, 165.1, 142.9, 137.2, 128.9, 128.2, 127.5, 127.1, 76.0, 62.8, 44.9, 13.7.

dx.doi.org/10.1021/jo502265a | J. Org. Chem. 2015, 80, 628−633

4-Benzoyl-4-deutero-3-(dideuteromethylene)-1-(*p*-tolyl)-azetidin-2-one (6). White solid (36 mg, 65%): mp 122−124 °C. ^{1}H NMR (400 MHz, CDCl3): δ 8.05 (d, J = 7.2 Hz, 2H), 7.68 (t, J = 7.2 Hz, 1H), 7.56 (t, J = 7.2 Hz, 2H), 7.23 (d, J = 8.4 Hz, 2H), 7.11 (d, J = 8.0 Hz, 2H), 2.29 (s, 3H); ^{13}C NMR (100 MHz, CDCl3): δ 191.5, 159.0, 143.8, 135.1, 134.55, 134.46, 134.2, 129.7, 129.2, 128.6, 116.9, 111.1 (qunit, J = 25.0 Hz), 63.6 (t, J = 23.5 Hz), 21.0; IR (KBr): ν (cm^{-1}) 2923, 1746, 1690, 1516, 1382, 1272, 1170, 920, 691; ESI-MS: (m/z) 281.2 (M^+ + H); HRMS calcd for $C_{18}H_{12}D_3NO_2$ (M + Na): 303.1183, found 303.1177.

■ ASSOCIATED CONTENT

Supporting Information

^{1}H and ^{13}C NMR spectra of all compounds (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: clig@mail.sioc.ac.cn (C.L.).

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

This project was supported by the National Natural Science Foundation of China (Grants 21228202, 21272259, 21290180, 21472220, and 21361140377) and by the National Basic Research Program of China (973 Program) (Grant 2011CB710805).

■ REFERENCES

(1) (a) Mobashery, S.; Meroueh, S. O.; Fisher, J. F. *Chem. Rev.* **2005**, *105*, 395. (b) Alcaide, B.; Almendros, P.; Aragocillo, C. *Chem. Rev.* **2007**, *107*, 4437. (c) Singh, G. S.; Sudleesh, S. In *Natural Lactones and Lactams: Synthesis, Occurrence and Biological Activity*; Janecki, T., Ed.; Wiley-VCH: Weinheim, Germany, 2014; Chapter 3, pp 101−145.

(2) (a) Tanaka, K.; Shoji, J.; Terui, Y.; Tsuji, N.; Kondo, E.; Mayama, M.; Kawamura, Y.; Hattori, T.; Matsumoto, K.; Yoshida, T. *J. Antibiot.* **1981**, *34*, 909. (b) Arisawa, M.; Then, R. L. *J. Antibiot.* **1982**, *35*, 1578.

(3) For a comprehensive review, see: Pitts, C. R.; Lectka, T. *Chem. Rev.* **2014**, *114*, 7930.

(4) For recent representative examples, see: (a) Crisp, G. T.; Meyer, A. G. *Tetrahedron* **1995**, *51*, 5585. (b) Anklam, S.; Liebscher, J. *Tetrahedron* **1998**, *54*, 6369. (c) Torchiarolo, G. C.; D'Onofrio, F.; Margarita, R.; Parlanti, L.; Piancatelli, G.; Bella, M. *Tetrahedron* **1998**, *54*, 15657. (d) Adam, W.; Groer, P.; Humpf, H.-U.; Saha-Möller, C. R. *J. Org. Chem.* **2000**, *65*, 4919. (e) Bella, A. F.; Jackson, L. V.; Walton, J. C. *Org. Biomol. Chem.* **2004**, *2*, 421. (f) Chen, H.-Y.; Patkar, L. N.; Ueng, S.-H.; Lin, C.-C.; Lee, A. S.-Y. *Synlett* **2005**, 2035. (g) Tiwari, D. K.; Shaikh, A. Y.; Pavase, L. S.; Gumaste, V. K.; Deshmukh, A. R. A. S. *Tetrahedron* **2007**, *63*, 2524. (h) Liang, Y.; Raju, R.; Le, T.; Taylor, C. D.; Howell, A. R. *Tetrahedron Lett.* **2009**, *50*, 1020. (i) Fujiwara, S.-i.; Shimizu, Y.; Imahori, Y.; Toyofuku, M.; Shin-ike, T.; Kambe, N. *Tetrahedron Lett.* **2009**, *50*, 3628. (j) Bari, S. S.; Arora, R.; Bhalla, A.; Venugopalan, P. *Tetrahedron Lett.* **2010**, *51*, 1719. (k) Lee, S. I.; Moon, S. Y.; Hwang, G.-S.; Ryu, D. H. *Org. Lett.* **2010**, *12*, 3234. (l) Bukovec, C.; Kazmaier, U. *Org. Biomol. Chem.* **2011**, *9*, 2743. (m) Bakthadoss, M.; Srinivasan, J.; Selvakumar, R. *Aust. J. Chem.* **2014**, *67*, 295. (n) Li, W.; Liu, C.; Zhang, H.; Ye, K.; Zhang, G.; Zhang, W.; Duan, Z.; You, S.; Lei, A. *Angew. Chem., Int. Ed.* **2014**, *53*, 2443.

(5) (a) Zhao, Q.; Li, L.; Fang, Y.; Sun, D.; Li, C. *J. Org. Chem.* **2009**, *74*, 459. (b) Chen, L.; Shi, M.; Li, C. *Org. Lett.* **2008**, *10*, 5285. (c) Zhao, Q.; Li, C. *Org. Lett.* **2008**, *10*, 4037. (d) Fang, Y.; Li, C. *J. Am. Chem. Soc.* **2007**, *129*, 8092. (e) Lu, H.; Li, C. *Org. Lett.* **2006**, *8*, 5365.

(6) For reviews, see: (a) Lu, X.; Zhang, C.; Xu, Z. *Acc. Chem. Res.* **2001**, *34*, 535. (b) Valentine, D. H., Jr.; Hillhouse, J. H. *Synthesis* **2003**, 317. (c) Methot, J. L.; Roush, W. R. *Adv. Synth. Catal.* **2004**, *346*, 1035. (d) Lu, X.; Du, Y.; Lu, C. *Pure Appl. Chem.* **2005**, *77*, 1985. (e) Nair, V.; Menon, R. S.; Sreekanth, A. R.; Abhilash, N.; Biju, A. T. *Acc. Chem. Res.* **2006**, *39*, 520. (f) Ye, L.-W.; Zhou, J.; Tang, Y. *Chem. Soc. Rev.* **2008**, *37*, 1140. (g) Fan, Y. C.; Kwon, O. *Chem. Commun.* **2013**, *49*, 11588.

(7) For the latest example, see: Deng, J.-C.; Kuo, C.-W.; Chuang, S.-C. *Chem. Commun.* **2014**, *50*, 10580.

(8) Representative examples: (a) Trost, B. M.; Dake, G. R. *J. Am. Chem. Soc.* **1997**, *119*, 7595. (b) Lecercle, D.; Sawicki, M.; Taran, F. *Org. Lett.* **2006**, *8*, 4283.

(9) Inanaga, J.; Baba, Y.; Hanamoto, T. *Chem. Lett.* **1993**, 241.

(10) Hess, W.; Burton, J. W. *Adv. Synth. Catal.* **2011**, *353*, 2966.

■ NOTE ADDED AFTER ASAP PUBLICATION

This paper was published ASAP on November 26, 2014. Equation 2 was updated. The revised paper was reposted on December 3, 2014.