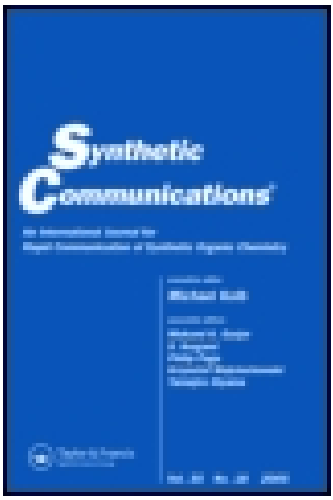

Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry
Publication details, including instructions for authors and subscription information:
http://www.tandfonline.com/loi/lsyc20

A Facile Conversion of 2-Substituted Acrylamides to 1,3-Disubstituted 3-Bromo-2-azetidinones

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Published online: 23 Sep 2006.

To cite this article: Sigeru Torii, Hiroshi Okumoto & Hidehiko Yabuki (1993) A Facile Conversion of 2-Substituted Acrylamides to 1,3-Disubstituted 3-Bromo-2-azetidinones, Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry, 23:4, 517-523, DOI: 10.1080/00397919308009807

To link to this article: http://dx.doi.org/10.1080/00397919308009807

SYNTHETIC COMMUNICATIONS, 23(4), 517-523 (1993)

A FACILE CONVERSION OF 2-SUBSTITUTED ACRYLAMIDES TO 1,3-DISUBSTITUTED 3-BROMO-2-AZETIDINONES

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Abstract: *N*-Substituted 2,3-dibromo-2-alkylacrylamides obtained by the bromination of 2-alkylacrylamides were converted to 1,3-disubstituted 3-bromo-2-azetidinones in excellent yields upon treatment with potassium carbonate in acetone under refluxing.

The clinical utility of β-lactam antibiotics is still expanding, and a new class of monocyclic β-lactam is under intensive research demanding a simple and convenient preparative way.[1] A lot of efforts have been devoted to the development of synthetic reactions, methodologies, and reagents. One of the efficient paths to the β-lactam skeleton is a bond making between N1 and C4 positions. Typically, substitution of leaving group at C3 with N1 nucleophile is performed, wherein the amide group is usually activated to increase the acidity and/or the nucleophilicity by sulfur or oxygen

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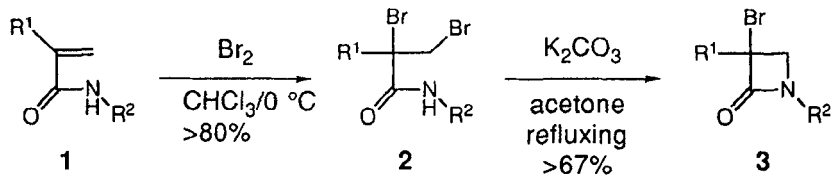
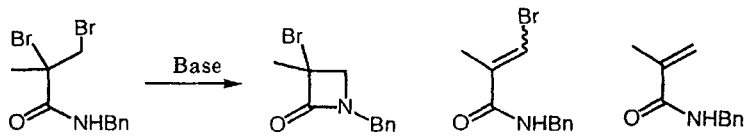
functionalities on the nitrogen atom which must be removed afterwards.[2] On the other hand, we have reported a direct synthesis of 2-substituted acrylamides by the palladium-catalyzed carbonylation of terminal acetylenes.[3] The convenient reaction promoted us to exploit a facile route to β-lactam **3** from the 2-substituted acrylamides **1** *via* two steps without activation of the amide group. Hence, direct introduction of a substituent on the nitrogen atom of β-lactam ring could be achieved. As outlined in the following scheme, our route involves only simple procedures and practical reagents and the yields are high.[4]



1 **2** **3**

Addition of bromine to **1** in chloroform at 0 °C gave the dibromide **2** in high yields. Subsequent treatment of the dibromide **2** with base afforded the β-lactam compound **3**. The cyclization of benzyl amide **2a** under a variety of conditions is collected in Table I. The employment of potassium carbonate in acetone under refluxing was found to be the best choice (Entry 1). The reaction with sodium hydride in THF at 0 °C also provided the expected compound **3a** in a comparable yield (Entry 2). However, elimination of hydrogen bromide, giving 3-bromomethacrylamide **4a**, proceeded in some extent upon treatment with sodium methoxide (Entry 3) or fluoride bases such as tetrabutylammonium or potassium fluoride (Entries 4

Table I Cyclization of the Dibromide **2 a**



2 a **3 a** **4 a** **1 a**

Entry	Base	Solvent	Temp. / Time	Yield, · %			
				2 a	**3 a**	**4 a**	**1 a**
1	K_2CO_3	acetone	reflux / 24h	0	93	1	0
2	NaH	THF	0 °C / 0.5 h	0	90	2	0
3	NaOMe	MeOH	r.t. / 18 h	0	20	42	7
4	Bu_4NF	THF	r.t. / 72 h	23	41	21	0
5	KF	DMSO	r.t. / 51 h	58	0	24	0
6	n-BuLi	THF	-78 °C / 1 h	39	0	0	52

and 5). Exposure of **2a** to butyllithium at -78 °C caused lithiation followed by elimination leading to the methacrylamide **1a** (Entry 6).

Several examples of the conversions of the amide **1** to the β-lactam **3** through the dibromide **2** under the optimized conditions are summarized in Table II. Thus, useful appendages at N1 to elaborate further functionalizations could be successfully utilized. Although the methacrylamide **1b** underwent bromination at the aromatic nucleus of *p*-methoxybenzyl group to give **2b** (Entry 2), *p*-methoxyphenyl amide **1c** was converted to **2c** without such a trouble (Entry 3). The ensuing cyclization of both dibromoamides **2b** and **2c**

Table II Conversion of Amides to β-Lactams

Entry	Amide, **1**	**2**, %[a]	**3**, %[b]
1	**a** : R^1=Me; R^2 = Bn	99	93
2	**b** : R^1=Me; R^2 = CH_2-C$_6$H$_4$-OMe	88 [c]	80[c]
3	**c** : R^1=Me; R^2 = C$_6$H$_4$-OMe	69	67
4	**d** : R^1=Me; R^2 = CH_2COOMe	85	83
5	**e** : R^1= $THPOCH_2$; R^2 = Bn	85	82

a) Carried out with Br_2 (2 equiv.) in $CHCl_3$.
b) Carried out with K_2CO_3 (2 equiv.) in acetone under refluxing.
c) **2b** and **3b** : R^2 = CH_2-C$_6$H$_3$(Br)-OMe

afforded the lactams **3b** and **3c**. The transformation of the other amides **1d** and **1e**, having functional groups such as ester and pyranyl ether groups, to the corresponding β-lactams **3d** and **3e** was attained in high yields (Entries 4 and 5).

The delineated sequences can be carried out without employing any cumbersome procedures, expensive reagents, and special care, and the starting materials are readily accessible. Furthermore, since a variety of elaborations of β-lactam compounds, including removal of the bromine atom at 3 position, have already been innovated in our group,[5] this method would provide an extremely convenient route to β-lactam antibiotics.

Experimental

^1H and ^{13}C NMR spectra were recorded in $CDCl_3$ on a Varian VXR-200 spectrometer (200 MHz for ^1H and 50 MHz for ^{13}C). The

chemical shifts and the coupling constants are reported in ppm and herz respectively. IR spectra were measured on a JASCO FT/IR-5000 and the data are expressed in cm^{-1}. The amides **1** were prepared either by the carbonylation of acetylenes[3] or by the reaction of methacryloyl chloride with amines in a conventional manner. Every reagents were used as received.

A Representative Procedure of the Bromination:

To a mixture of *N*-benzyl methacrylamide (**1a**) (175 mg, 1.00 mmol) and sodium acetate (410 mg, 3.02 mmol) in chloroform (5 mL) was added dropwise bromine (0.10 mL, 2.00 mmol) at 0°C under argon atmosphere. After being stirred for 20 min, the mixture was poured into a solution of 10% sodium thiosulfate, and then extracted with ethyl acetate three times. The extracts were washed with brine, dried over sodium sulfate, and concentrated under reduced pressure. The crude products were purified by column chromatography on silica gel to afford the dibromide **2a** (331 mg, 99%). IR (KBr) 3304, 3032, 1653; ^{1}H NMR δ 2.08 (s, 3H), 3.95 (ABq, J = 11.2, 2H), 4.34-4.63 (m, 2H), 6.82-7.06 (br, 1H), 7.24-7.42 (m, 5H); ^{13}C NMR δ 29.00, 41.04, 44.47, 63.22, 127.59, 127.67, 128.74, 137.27, 168.46.

***N*-3-Bromo-4-methoxybenzyl 2,3-dibromo-2-methylpropionamide (2b):** IR (KBr) 3310, 1653; ^{1}H NMR δ 2.02 (s, 3H), 3.93 (s, 2H), 4.25-4.50 (m, 2H), 6.83 (d, J = 8.4, 1H), 7.18 (dd, J = 8.4, 2.0, 1H), 7.46 (d, J = 2.0, 1H); ^{13}C NMR δ 28.72, 40.78, 43.22, 56.20, 62.64, 111.62, 111.94, 127.78, 130.92, 132.47, 155.23, 168.48.

***N*-4-Methoxyphenyl 2,3-dibromo-2-methylpropionamide (2c):** IR (KBr) 3296, 1653; ^{1}H NMR δ 2.11 (s, 3H), 3.76 (s, 3H), 3.94, 4.02 (ABq, J = 10.0, 2H), 6.75-6.88 (m, 2H), 7.35-7.45 (m, 2H), 8.25-8.45 (br, 1H); ^{13}C NMR δ 28.67, 40.79, 55.32, 63.04, 113.98, 122.44, 129.73, 156.93, 166.47.

***N*-Methoxycarbonylmethyl 2,3-dibromo-2-methylpropionamide (2d):** IR (KBr) 3300, 3048, 1744, 1659; ^{1}H NMR δ 2.03 (s, 3H), 3.70 (s, 3H), 3.90 (s, 2H), 4.03 (d, J = 5.9, 2H), 6.99-7.23 (br, 1H); ^{13}C NMR δ 28.40, 40.39, 41.93, 52.37, 61.47, 168.74, 169.50.

***N*-Benzyl 2,3-dibromo-2-(tetrahydropyranyl-2-oxymethyl)-propionamide (2e) (diastereomeric mixture) :** IR (neat) 3342, 1665, 1537; ^{1}H NMR δ 1.3-1.9 (m, 6H), 3.4-4.72 (m, 10H) 7.2-7.4 (m, 5H); ^{13}C

NMR δ 18.72, 18.89, 25.00, 25.10, 29.94, 30.02, 35.81, 36.32, 44.21, 62.07, 62.25, 63.84, 64.74, 71.21, 71.55, 98.54, 99.32, 127.49, 127.54, 127.66, 128.62, 137.33, 166.67, 166.79.

A Typical Procedure of the Cyclization:

A mixture of the dibromide **2a** (168 mg, 0.50 mmol) and potassium carbonate (139 mg, 1.01 mmol) in acetone (5 mL) was heated to reflux for 24 h under argon atmosphere. After being cooled to room temperature, the mixture was filtered through a short silica gel column. The filtrates were concentrated under reduced pressure, and then the residue was purified by column chromatography on silica gel to afford the β-lactam **3a** (119 mg, 93%). IR (neat) 3034, 1767, 1605; ^{1}H NMR δ 1.88 (s, 3H), 3.45 (ABq, J = 6.1, 2H), 4.39 (s, 2H), 7.16-7.41 (m, 5H); ^{13}C NMR δ 24.77, 45.87, 57.29, 57.94, 127.88, 128.84, 134.39, 166.66.

1-(3-Bromo-4-methoxybenzyl)-3-bromo-3-methylazetidin-2-one (3b): IR (neat) 1767, 1605; ^{1}H NMR δ 1.89 (s, 3H), 3.37, 3.53 (ABq, J = 6.1, 2H), 3.88 (s, 3H), 4.31 (ABq, J = 16.3, 2H), 6.87 (d, J = 8.5, 1H), 7.15 (dd, J = 8.5, 3.3, 1H), 7.39 (d, J = 3.3, 1H); ^{13}C NMR δ 24.81, 44.83, 56.23, 57.31, 57.95, 111.90, 112.19, 127.96, 128.26, 132.93, 155.63, 166.65.

1-(4-Methoxyphenyl)-3-bromo-3-methylazetidin-2-one (3c): IR (KBr) 1754, 1518; ^{1}H NMR δ 2.01 (s, 3H), 3.79 (s, 3H), 3.87, 4.01 (ABq, J = 6.3, 2H), 6.85-6.91 (m, 2H), 7.26-7.32 (m, 2H); ^{13}C NMR δ 25.16, 55.48, 57.04, 57.19, 114.49, 117.97, 131.03, 156.67, 162.90.

1-Methoxycarbonylmethyl-3-bromo-3-methylazetidin-2-one (3d): IR (neat) 1748; ^{1}H NMR δ 1.94 (s, 3H), 3.74 (s, 3H), 3.72, 3.79 (ABq, J = 5.8, 2H), 3.86, 4.17 (ABq, J = 18.1, 2H); ^{13}C NMR δ 24.84, 42.76, 52.46, 58.20, 58.86, 167.19, 168.04.

1-Benzyl-3-bromo-3-(tetrahydropyranyl-2-oxymethyl)azetidin-2-one (3e) (diastereomeric mixture) : IR (neat) 1771; ^{1}H NMR δ 1.4-1.9 (m, 6H), 3.4-4.7 (m, 9H), 7.2-7.4 (m, 5H); ^{13}C NMR δ 18.52, 19.21, 25.12, 29.90, 30.15, 46.08, 46.11, 52.36, 52.51, 59.16, 59.37, 61.40, 62.39, 67.55, 67.59, 98.31, 99.01, 127.86, 128.71, 128.75, 134.51, 164.80, 165.01.

SC-NMR Laboratory of Okayama University is appreciated for obtaining high resolution NMR spectra.

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(Accepted in Japan 5 September, 1992)