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Rapid Synthesis of 1,3,4,4-Tetrasubstituted β-Lactams from Methyleneaziridines Using a Four-Component Reaction‡

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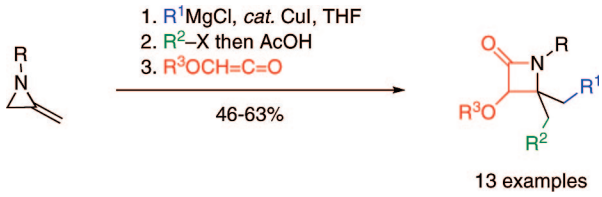

2-Methyleneaziridines can be transformed into a variety of 1,3,4,4-tetrasubstituted β-lactams in moderate to good yields (46−63%) via a "one-pot" process that brings together four components with the formation of three new intermolecular carbon−carbon bonds.

Multicomponent reactions (MCRs) are one-pot processes that bring together three or more starting materials to form a product that contains most if not all elements of the reactants.[1,2] They represent a fundamentally more efficient approach to chemical synthesis than traditional bimolecular reactions. Important examples include the Ugi, Passerini, Strecker, and Biginelli reactions. MCRs have emerged as powerful tools for drug discovery because of their ability to produce small druglike molecules with several degrees of structural diversity via single transformations.[3]

β-Lactams are an important class of heterocycles that are renowned for their potent antibiotic activity.[4,5] They also serve as useful building blocks for the synthesis of other classes of compounds.[6] Taken together, these factors have encouraged researchers to search for MCR methods for the efficient synthesis of libraries of β-lactams, and some notable successes have been achieved.[7]

Over the past few years, a powerful new MCR based upon the highly strained 2-methyleneaziridine ring system has been developed in our laboratory.[8] The reaction involves ring opening of methyleneaziridine **1** at C-3 using a Grignard reagent under Cu(I) catalysis and capture of the resultant metalloenamine with a carbon-based electrophile (R^2X). By combining this approach to ketimines with a Staudinger $[2\pi + 2\pi]$ cycloaddition,[9,10] we reasoned that it might be possible to develop a flexible approach to 1,3,4,4-tetrasubstituted β-lactams (Scheme 1). Several features of this sequence are especially noteworthy. This four-component reaction (4-CR) creates three new intermolecular C−C bonds via a "one-pot" process and generates four points of chemical diversity. Moreover, since it creates one quaternary center[11] and one tertiary center, the products are expected to have considerable synthetic value.[12] In this paper, we report the successful development of this MCR approach to 1,3,4,4-tetrasubstituted β-lactams and outline its scope and limitations.

Three methyleneaziridines, namely **1a**−**c**, were prepared and used in this study. 1-(4-Methoxybenzyl)-2-methyleneaziridine

‡ This paper is dedicated to the memory of Professor A. I. Meyers.

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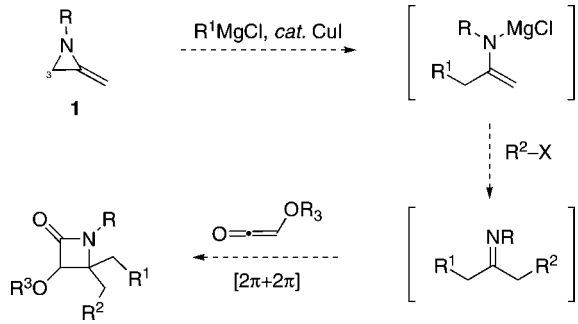
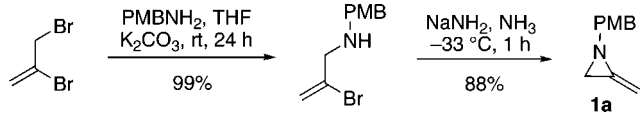
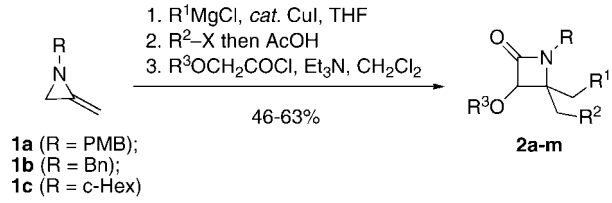
SCHEME 1. MCR Approach to β-Lactams



SCHEME 2. Synthesis of 2-Methyleneaziridine 1a



SCHEME 3. β-Lactam Synthesis by "One-Pot" 4-CR



(**1a**) was made in 87% yield from 2,3-dibromopropene and 4-methoxybenzylamine using a sodium amide induced ring closure (Scheme 2).[13] Aziridine **1a** was selected as *N*-deprotection of the PMB group in the resultant β-lactam was anticipated to be straightforward (vide infra).[14] 1-Benzyl-2-methyleneaziridine (**1b**) and 1-cyclohexyl-2-methyleneaziridine (**1c**) were made in a similar manner according to published methods.[15]

With methyleneaziridines **1a**−**c** in hand, conditions for effecting the MCR were developed. After some optimization, it was established that treatment of **1a** in THF with BnMgCl (3.0 equiv) and CuI (20 mol %) induced ring opening of the aziridine at C-3 to generate the metalloenamine, which was alkylated with BnBr (1.5 equiv). Subsequent addition of glacial acetic acid (2 equiv) and then (benzyloxy)ketene (generated from $BnOCH_2COCl$, Et_3N, −78 °C[16]) in CH_2Cl_2 yielded β-lactam **2a** in 50% yield after silica gel column chromatography (Scheme 3 and Table 1, entry 1). The structural changes arising from this "one-pot" sequence were verified by X-ray diffraction on a single crystal of **2a** grown from CH_2Cl_2/pentane (see Supporting Information). To test the scope of this 4-CR, β-lactams **2a**−**m** were synthesized by variation of the Grignard reagent,

TABLE 1. 4-Component β-Lactam Synthesis

entry	aziridine	R^1	R^2X	R^3	lactam	yield[a] (%)
1	**1a**	Bn	BnBr	Bn	**2a**	50
2	**1b**	Et	BnCl	Bn	**2b**	62
3	**1c**	Et	BnCl	Bn	**2c**	60
4	**1a**	Et	BnCl	Me	**2d**	55
5	**1a**	Bn	$CH_2{=}CHCH_2Br$	Bn	**2e**	49
6	**1a**	Bn	PMBCl	Bn	**2f**	58
7	**1a**	Et	MeI	Bn	**2g**	46
8	**1a**	Et	BnCl	Bn	**2h**	59
9	**1a**	Et	$THPO(CH_2)_3Br$	Bn	**2i**	63[b]
10	**1a**	Et	$CH_3C{\equiv}CCH_2Br$	Bn	**2j**	49
11	**1a**	Bu	BnBr	Bn	**2k**	54
12	**1a**	Bu	MeI	Bn	**2l**	55[b]
13	**1a**	^{i}Pr	BnCl	Bn	**2m**	47

[a] Isolated yield after aqueous workup and column chromatography. Unless otherwise noted, all compounds (except **2a**) were isolated as ca. 1:1 mixture of diastereomers as judged by ^{1}H NMR spectroscopy. Detailed experimental procedures and full characterization data are provided in the Supporting Information. [b] Combined yield of separated diastereomers.

electrophile, methyleneaziridine, and ketene components (Table 1). These studies reveal that this MCR tolerates changes in all four components, and that many common functional groups can be incorporated into the β-lactam products. The only significant byproduct observed was $R^1COCH_2OR^3$ derived from direct addition of the organometallic reagent to the ketene. By adding AcOH to destroy excess Grignard reagent prior to addition of the ketene, the yields of the β-lactam were improved in many cases by minimizing the formation of this byproduct. Lower yields were also noted if the RCOCl was added to a mixture of the ketimine and Et_3N rather than by preforming the ketene. In relation to changes in the Grignard and electrophile component, the scope of this reaction broadly parallels that found for the ketone MCR.[8c] Although the yields are quite modest (46−63%), the efficiency with respect to each individual C−C bond forming step is very good (77−86%/C−C bond). Little control over diasteroselectivity is observed with near equal quantities of the cis and trans diastereomers being produced.[17] This lack of stereocontrol is presumably because both α-carbons of the ketimine are structurally similar, resulting in little stereodifferentiation with respect to the approaching ketene. Despite this limitation, this method provides an efficient way to make a diverse range of racemic β-lactams.

To demonstrate the utility of the derived 1,3,4,4-tetrasubstituted β-lactams, diastereomerically pure *trans*-**2l**[18] was deprotected using cerium ammonium nitrate[14] by cleavage of the *p*-methoxybenzyl group to give *trans*-**3** in 59% yield (Scheme 4). Alternatively, the β-lactam ring of *trans*-**2l** can be ring-opened with methanol and trimethylsilyl chloride to provide diastereomerically pure β-amino ester **4** (Scheme 4).

To conclude, a versatile 4-CR has been developed for the rapid synthesis of 1,3,4,4-tetrasubstituted β-lactams from methyleneaziridines by the sequential formation of three C−C bonds through a sequence that involves aziridine opening, C-alkylation and Staudinger [2π + 2π] cycloaddition. Work to

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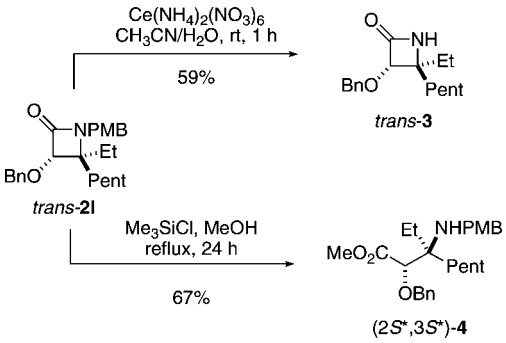
(17) Here, cis and trans are used to indicate the relative position of the "largest" carbon substituent at C-4 relative to the C-3 ether (OR^3).

(18) NOE difference measurements conducted on *trans*-**3** allowed its configuration to be established. Strong NOEs were observed between C*H*OBn and-C*H*$_2$(CH$_2$)$_3$CH$_3$ indicating a syn relationship between these substituents. Furthermore, CAN deprotection of *cis*-**2l** (details not shown) gave *cis*-**3**, which produced analogous NOEs between the C*H*OBn and−C*H*$_2$CH$_3$ hydrogens. The stereochemistries of *cis*- and *trans*-**2l** and (2*S**,3*S**)-**4** were derived by extrapolation of these findings.

SCHEME 4. Further Manipulations of β-Lactams



generate other important classes of compounds using methyleneaziridine MCRs continues in our laboratory.

Experimental Section

Synthesis of β-Lactams: General Procedure. Copper(I) iodide (ca. 20 mol %) in a round-bottomed flask was heated under vacuum and then purged with nitrogen (three cycles performed). Dry THF was added and the mixture cooled to −30 °C, whereupon the Grignard reagent (2.5−3.0 molar equiv) was added. After 10 min, methyleneaziridine **1** in THF was added, and the reaction mixture stirred at room temperature for 3 h. After the reaction mixture was cooled to 0 °C, the electrophile (1.5−2.0 molar equiv) was added dropwise, and the mixture heated at 40 °C for 3 h. After the reaction mixture was cooled to 0 °C, acetic acid (2 molar equiv) was added dropwise and the mixture stirred at room temperature for 30 min. In a separate round-bottomed flask, triethylamine (4.4 molar equiv) was added to a solution of the acid chloride (1.4 molar equiv) in CH_2Cl_2 at −78 °C. After 5 min, this mixture was added via cannula to the first reaction mixture at −78 °C. The resulting mixture was stirred overnight, during which time the temperature was allowed to rise to room temperature. The mixture was diluted with Et_2O (20 mL) and washed with water (5 mL), 0.1 M HCl (5 mL), and a saturated aqueous solution of $NaHCO_3$ (5 mL). The organic phase was dried over $MgSO_4$, filtered, and concentrated in vacuo. Purification of the β-lactam was achieved by column chromatography.

3-Benzyloxy-1-(4-methoxybenzyl)-4,4-diphenylethylazetidin-2-one (2a). β-Lactam **2a** was prepared from CuI (22 mg, 0.12 mmol) in THF (2 mL), benzylmagnesium chloride (2.0 M in THF, 860 μL, 1.72 mmol), methyleneaziridine **1a** (100 mg, 0.57 mmol) in THF (1 mL), benzyl bromide (102 μL, 0.86 mmol), acetic acid (65 μL, 1.14 mmol), benzyloxyacetyl chloride (120 μL, 0.76 mmol), and triethylamine (350 μL, 2.51 mmol) in CH_2Cl_2 (2.5 mL) according to the general procedure. Workup followed by column chromatography (petroleum ether:ethyl acetate, 5:1, R_f = 0.22) afforded **2a** (145 mg, 50%) as a white solid: mp 88−90 °C; IR (film) 2951, 2931, 2856, 1744, 1608, 1509, 1453 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) 7.45−7.10 (13H, m), 6.95 (4H, d, J = 7.5 Hz), 6.88 (2H, d, J = 8.5 Hz), 4.94 (1H, d, J = 11.8 Hz), 4.66 (1H, d, J = 11.8 Hz), 4.43 (1H, s), 4.34 (1H, d, J = 15.6 Hz), 4.30 (1H, d, J = 15.6 Hz), 3.79 (3H, s), 2.66 (1H, dt, J = 12.8, 5.0 Hz), 2.58−2.44 (2H, m), 2.39−2.32 (1H, dt, J = 12.6, 5.0 Hz), 2.10−1.89 (3H, m), 1.77−1.65 (1H, m); ^{13}C NMR (100 MHz, $CDCl_3$) 167.7 (C), 159.4 (C), 142.1 (C), 140.9 (C), 137.4 (C), 129.8 (CH), 129.1 (C), 128.6 (CH), 128.5 (CH), 128.4 (CH), 128.3 (CH), 128.2 (CH), 128.1 (CH), 128.0 (CH), 126.3 (CH), 125.9 (CH), 114.3 (CH), 85.7 (CH), 73.2 (CH_2), 67.7 (C), 55.4 (CH_3), 43.1 (CH_2), 37.6 (CH_2), 35.6 (CH_2), 30.8 (CH_2), 30.6 (CH_2); MS (ES^+) m/z = 506 ($[M + H]^+$, 100); HRMS (ES^+) m/z calcd for $C_{34}H_{35}NNaO_3$ $(M + Na)^+$ 528.2515, found 528.2509.

3-Benzyloxy-1-cyclohexyl-4-phenylethyl-4-propylazetidin-2-one (2c). β-Lactam **2c** was prepared from CuI (28 mg, 0.15 mmol) in THF (2 mL), ethylmagnesium chloride (2.0 M in THF, 1.20 mL, 2.40 mmol), methyleneaziridine **1c** (109 mg, 0.79 mmol) in THF (1 mL), benzyl chloride (190 μL, 1.65 mmol), acetic acid (90 μL, 1.57 mmol), benzyloxyacetyl chloride (180 μL, 1.14 mmol), and triethylamine (490 μL, 3.52 mmol) in CH_2Cl_2 (2.5 mL) according to the general procedure. Workup followed by column chromatography (petroleum ether/ethyl acetate, 8:1, R_f = 0.21) afforded **2c** (191 mg, 60%) as a pale yellow oil as ca. 1:1 mixture of diastereomers as judged by ^1H NMR spectroscopy: IR (film) 2927, 2856, 1736, 1601, 1493, 1453 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) 7.46−7.03 (10H, m), 4.90 (0.5H, d, J = 11.8 Hz), 4.84 (0.5H, d, J = 11.8 Hz), 4.67 (0.5H, d, J = 11.8 Hz), 4.62 (0.5H, d, J = 11.8 Hz), 4.24 (0.5H, s), 4.20 (0.5H, s), 3.07−2.87 (1H, m), 2.84−2.65 (1H, m), 2.64−2.54 (0.5H, m), 2.52−2.39 (0.5H, m), 2.20−1.09 (16H, m), 1.06−0.85 (3H, m); ^{13}C NMR (100 MHz, $CDCl_3$) 166.9 (C), 166.8 (C), 142.3 (C), 141.3 (C), 137.7 (C), 137.6 (C), 128.7 (CH), 128.49 (CH), 128.45 (CH), 128.42 (CH), 128.3 (CH), 128.2 (CH), 127.89 (CH), 127.86 (CH), 127.8 (CH), 126.3 (CH), 126.0 (CH), 85.6 (CH), 85.4 (CH), 73.0 (CH_2), 72.9 (CH_2), 67.35 (C), 67.31 (C), 53.4 (CH), 53.3 (CH), 38.5 (CH_2), 38.1 (CH_2), 36.0 (CH_2), 35.7 (CH_2), 32.1 (CH_2), 31.9 (CH_2), 31.73 (CH_2), 31.68 (CH_2), 31.0 (CH_2), 25.93 (CH_2), 25.87 (CH_2), 25.21 (CH_2), 25.17 (CH_2), 17.9 (CH_2), 17.8 (CH_2), 15.0 (CH_3), 14.6 (CH_3); MS (ES^+) m/z = 406 ($[M + H]^+$, 100); HRMS (ES^+) m/z calcd for $C_{27}H_{35}$ $NNaO_2$ $(M + Na)^+$ 428.2565, found 428.2560.

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Supporting Information Available: Characterization data and ^1H and ^{13}C NMR spectra for compounds **1a**, **2a**−**m**, **3**, and **4**, experimental procedures for their preparation, and X-ray data for **2a**. This material is available free of charge via the Internet at http://pubs.acs.org.

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