

Synthesis of Structurally Diverse 2-Azetidinones via Staudinger Reaction on a Solid Support

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Trimellitic anhydride was attached to Merrifield resin and a ketene was generated from polymer-bound phthaloylglycine. Then this polymer reacted with imines in the presence of Vilsmeier reagent and triethylamine to afford the solid-phase-tethered β-lactam products. Selective cleavage of supported β-lactams by trifluoroacetic acid and methylhydrazine gave 4-carboxyphthalimido- and 3-amino-β-lactams, respectively. The *trans*-stereochemistry was found in all products.

The β-lactam unit is the key structural element of the most widely employed family of β-lactam antibiotics and is responsible for the observed biological activity. These miracle drugs have improved the health and life expectancy of humans.[1] In addition to their well-recognized properties as antibiotics, β-lactams have been recently shown to possess other relevant biological activities.[2] On the other hand, the use of 2-azetidinones as building blocks in organic synthesis and semi-synthesis of Taxol derivatives is now well established.[3]

Building of the β-lactam (2-azetidinone) ring is a crucial step in the synthesis of new β-lactam antibiotics, and development of new preparative approaches toward β-lactam cycles is highly important.[4] Among several methods for the synthesis of β-lactams,[5] the [2 + 2] cycloaddition reaction of Schiff bases with ketenes (Staudinger reaction)[6] is mostly applied.[7]

The use of polymeric supports in organic synthesis has become a common practice, especially following the rapid development of combinatorial chemistry.[8] Primarily, the uses of polymers in synthesis have fallen into one of two areas: (A) the use of the polymer as a support for reactants or (B) the use of the polymer as support for reagents and catalysts during a reaction.[9] IR spectroscopy is a fast and simple method for the qualitative detection of certain functional groups on insoluble supports.[10]

Interest in solid-phase heterocyclic chemistry originated mainly in the pharmaceutical industry. Several review articles have appeared covering the synthesis of heterocycles on insoluble supports for the production of compound libraries for drug discovery.[11] One of the support types most frequently used for solid-phase organic synthesis are styrene–divinylbenzene copolymers (crosslinked polystyrene).[12] Chloromethyl polystyrene (Merrifield resin)[13] has been used widely in the polymer-supported synthesis of organic compounds.[12] It is commercially available and also has been prepared by several methods.[14]

The application of combinatorial and related methodologies to the chemistry of the β-lactam ring is a very attractive challenge to modern medicinal chemistry, a fact that has been recognized by different research groups around the world.[15] In the polymer-supported synthesis of β-lactams, the methods reported in Ref. 5 have been used whereas one of the reactants or reagent has been supported on soluble or insoluble polymer.[16]

Herein, we summarize our efforts directed toward the development of a new method for the synthesis of β-lactams via ketene–imine cycloaddition using polymer-supported ketene. This paper further deals with the methods for deprotection of products from polymer.

Trimellitic anhydride was easily linked to Merrifield resin via a classical synthetic method using triethylamine as a base to give the polymer-supported trimellitic anhydride **1**. The chemical reaction was monitored by IR spectroscopy which showed definitely the ester and anhydride functional groups. Then the Merrifield resin-bound anhydride **1** reacted with glycine in refluxing toluene for 24 h to afford polymer-supported phthaloylglycine **2** (Scheme 1). The appearance of carbonyl and hydroxy groups of COOH in the IR spectrum confirmed the structure of **2**.

The Staudinger reaction was used for the generation of the β-lactam ring. The [2 + 2] cycloaddition was performed by adding imines **3a**–**3i**, (chloromethylene)dimethylammonium chloride (Vilsmeier reagent) (**4**), and triethylamine in excess to a suspention of **2** in dry CH_2Cl_2 at room temperature to afford polymer-supported β-lactams **5a**–**5i**. In all cases the IR spectra of polymer-supported β-lactams **5a**–**5i** definitely showed the carbonyl group of the 2-azetidinone ring at 1775–1781 cm^{-1}.

In the next step, the polymer-supported β-lactams **5a**–**5i** were cleaved by two methods, ester-bond cleavage and dephthalation. The libraries of β-lactam compounds have been developed using this solid-phase strategy (Table 1 and Table 2). Overall yields ranged from good to very good for the four-step synthetic sequence and exclusive formation of the

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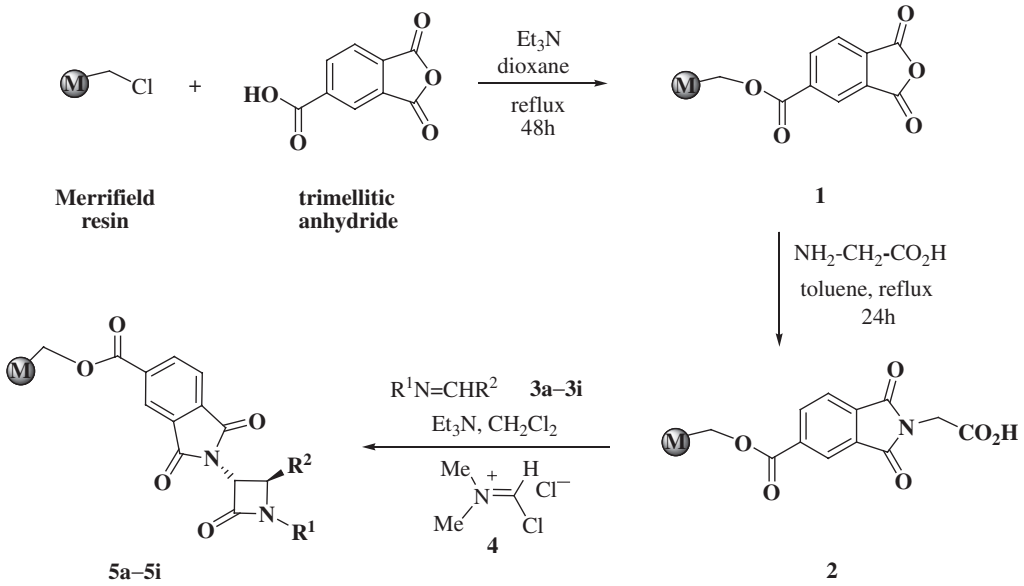


Scheme 1.

Table 1. Cleavage of the Resin-Bound β-Lactams **5a–5i** with TFA or $AlCl_3$

Product	R^1	R^2	Yield/%[a]	
			TFA	$AlCl_3$
6a	4-$EtOC_6H_4$	4-MeC_6H_4	68	49
6b	4-$EtOC_6H_4$	4-$NO_2C_6H_4$	71	46
6c	4-$EtOC_6H_4$	4-ClC_6H_4	66	45
6d	4-$EtOC_6H_4$	4-$MeOC_6H_4$	78	46
6e	C_6H_5	4-$MeOC_6H_4$	73	53
6f	C_6H_5	C_6H_5	64	50
6g	4-$MeOC_6H_4$	4-$MeOC_6H_4$	75	55
6h	$C_6H_5CH_2$	4-$NO_2C_6H_4$	72	51
6i	4-($C_6H_5N{=}N)C_6H_4$	4-ClC_6H_4	70	48

a) Overall isolated yield (based on the initial loading level of Merrifield resin).

Table 2. Dephthalation of the Resin-Bound β-Lactams **5a–5i** with $MeNHNH_2$

Product	R^1	R^2	Yield/%[a]
8a	4-$EtOC_6H_4$	4-MeC_6H_4	58
8b	4-$EtOC_6H_4$	4-$NO_2C_6H_4$	61
8c	4-$EtOC_6H_4$	4-ClC_6H_4	53
8d	4-$EtOC_6H_4$	4-$MeOC_6H_4$	56
8e	C_6H_5	4-$MeOC_6H_4$	58
8f	C_6H_5	C_6H_5	50
8g	4-$MeOC_6H_4$	4-$MeOC_6H_4$	51
8h	$C_6H_5CH_2$	4-$NO_2C_6H_4$	55
8i	4-($C_6H_5N{=}N)C_6H_4$	4-ClC_6H_4	53

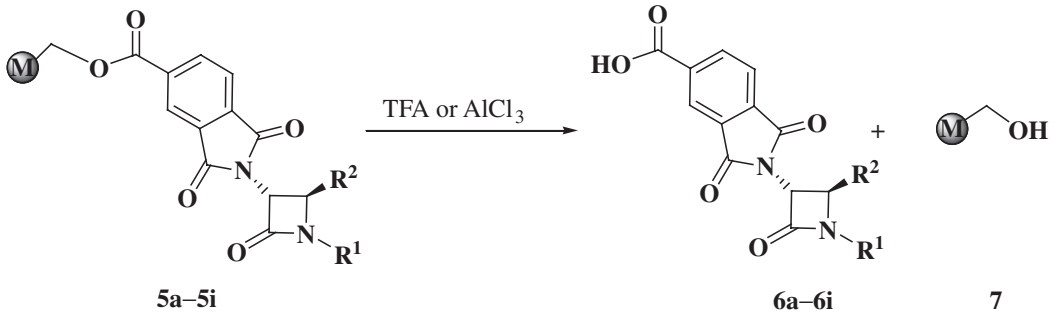
a) Overall isolated yield (based on the initial loading level of Merrifield resin).

trans-isomer was detected in all cases. Different β-lactam derivatives with various substitutents at positions 1 and 4 were obtained including many potential intermediates for the synthesis of active compounds. For instance *p*-ethoxyphenyl, *p*-methoxyphenyl, *p*-chlorophenyl, *p*-nitrophenyl, and carboxyl group undergo facile functional group transformations, and free amino group at C-3 allows the introduction of amide side chain, present in most of the β-lactam antibiotics.

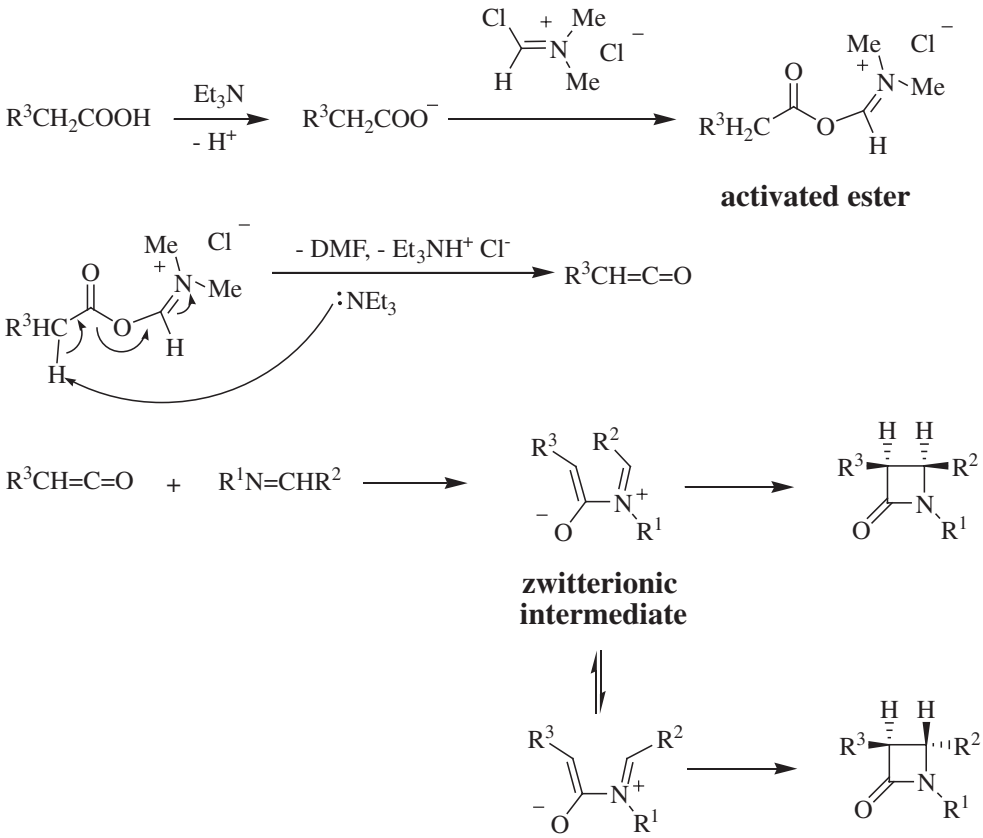
Cleavage of resins **5a–5i** using trifluoroacetic acid (TFA) or aluminum chloride ($AlCl_3$) resulted in the *trans*-4-carboxyphthalimido-β-lactams **6a–6i** (Scheme 2 and Table 1). While treatment with $AlCl_3$ gave 45–55% overall yield, use of 10% TFA in CH_2Cl_2 was found to be the most effective method for the cleavage, affording β-lactams **6a–6i** in 64–78% overall isolated yield (based on the loading of starting Merrifield resin). The presence of H-3, H-4, hydroxy group in ^{1}H NMR spectra and carboxyl group in IR spectra definitely confirmed the structure of β-lactams **6a–6i**.

trans-Stereochemistry was deduced from H-3 and H-4 coupling constants in ^{1}H NMR ($J \leq 2.5$ Hz). It is noteworthy that the preparation of the β-lactam ring via classical ketene–imine cycloaddition reaction leads to β-lactams with *cis*-selectivity[17] although *trans*-β-lactams have been obtained by other methods,[18] refluxing in toluene[19] and catalytic asymmetric Staudinger reaction.[20] The stereochemistry is mainly dominated by electronic effects and steric hindrance of ketene and imine substituents.[21] The *cis*-3-phthalimido-β-lactams have been previously synthesized via cycloaddition of imines and activated acetic acid derivatives[22] while the stereochemistry is all *trans* in this solid-supported method. The mechanism is perhaps similar to our previously reported mechanism for the Staudinger reaction from acetic acid derivatives and imines using methoxymethylene-*N*,*N*-dimethyliminium salt (Scheme 3).[23]

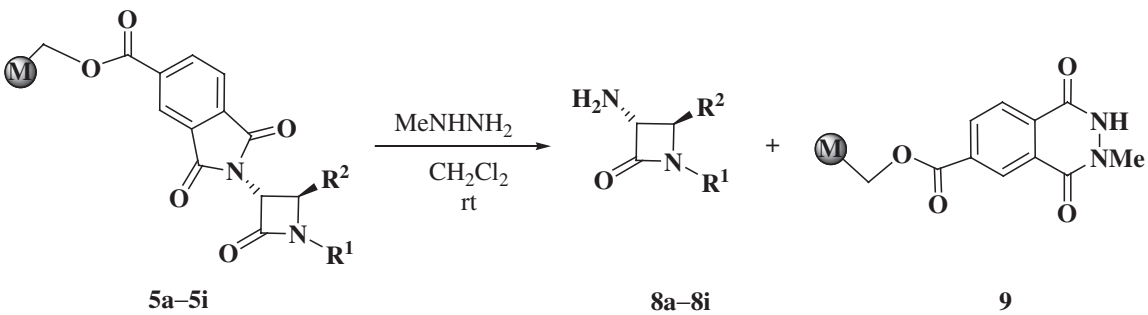
In another way, the polymer-supported β-lactams **5a–5i** were treated with methylhydrazine to give 3-amino-β-lactams **8a–8i** (Scheme 4 and Table 2). The appearance of NH_2 peaks in IR and ^{1}H NMR spectra confirmed the synthesis of 3-amino-β-lactams **8a–8i**. The polymer-supported 2-methylphthalazine-l,4(2*H*,3*H*)-dione **9** was cleaved by trifluoroacetic acid to hydroxymethyl resin **7**.



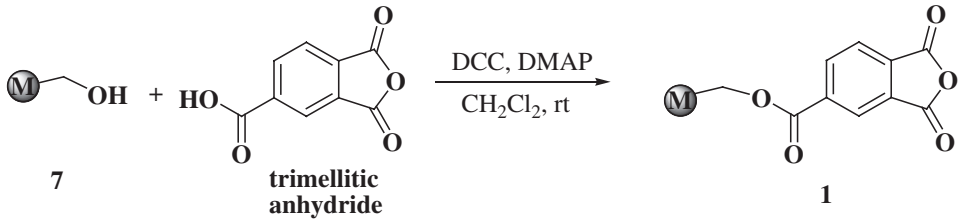
Scheme 2.



Scheme 3.



Scheme 4.



Scheme 5.

The resulting hydroxymethyl resin **7** was transformed to polymer-supported trimellitic anhydride **1** by dicyclohexylcarbodiimide (DCC) and trimellitic anhydride (Scheme 5).

Conclusion

In summary, we applied the Merrifield resin-bound phthaloylglycine for solid-phase polymer-supported synthesis of β-lactams. 4-Carboxyphthalimido- and 3-amino-β-lactams were obtained selectively by cleavage of supported β-lactam by trifluoroacetic acid and methylhydrazine, respectively. In this method, purification is facilated by simple filtration, avoiding time-consuming separation techniques; subsequent reactants and reagents can be added in excess to drive reactions to completion. The resulting hydroxymethyl resin from the cleavage stage was easily converted to starting Merrifield resin-bound phthaloylglycine in two steps.

Experimental

General. All required chemicals were purchased from Merck, Fluka, and Acros chemical companies. ^{1}H NMR and ^{13}C NMR spectra were recorded in DMSO-d_6 and $CDCl_3$ using a Bruker Avance DPX instrument (^{1}H NMR 250 MHz, ^{13}C NMR 62.9 MHz). Chemical shifts are reported in ppm (δ) downfield from TMS. All of the coupling constants (J) are in Hertz. The mass spectra were recorded on a Shimadzu GC-MS QP 1000 EX instrument. Elemental analyses were run on a Thermo Finnigan Flash EA-1112 series. Melting points were determined in open capillaries with a Buchi 510 melting point apparatus and are not corrected. Thin-layer chromatography was carried out on silica gel 254 analytical sheets obtained from Fluka.

Preparation of Polymer-Supported Trimellitic Anhydride 1. To the Merrifield resin (1.0 g, 1.2 mmol g^{-1}), swollen in dioxane (20 mL) were added the trimellitic anhydride (1,2,4-benzenetricarboxylic 1,2-anhydride) (0.9 g, 4.8 mmol) followed by Et_3N (1.7 mL, 12 mmol) and the reaction mixture was refluxed for 48 h. The reaction was filtered and the resin was washed with H_2O (60 mL), dioxane (60 mL), EtOH (60 mL), and CH_2Cl_2 (60 mL). The resin was dried by suction on a sinter glass. IR (KBr) cm^{-1}: 1724 (CO, ester), 1741, 1776 (CO, phth).

Preparation of Polymer-Supported Phthaloylglycine 2. Finely powdered glycine (0.27 g, 3.6 mmol) was added to a pre-swollen polymer-supported trimellitic anhydride **1** (1.0 g, 1.0 mmol g^{-1}, theoretical load) in toluene (20 mL). The mixture was refluxed for 24 h, filtered and the resin was washed with H_2O (60 mL), DMF (60 mL), EtOH (60 mL), and CH_2Cl_2 (60 mL). The resin was dried by suction on a sinter glass. IR (KBr) cm^{-1}: 1728 (CO, ester), 1743 (COOH), 1737, 1778 (CO, phth), 2840–3339 (OH).

General Procedure and Synthesis of Schiff Bases 3a–3i. A mixture of corresponding amine (10.0 mmol) and corresponding aldehyde (10.0 mmol) was refluxed in ethanol for 3 h. After cooling the solution, the precipitate was filtered and washed with ethanol to give pure Schiff bases **3a–3i**.

4-Ethoxyphenyl-*N*-(4-methylbenzylidene)amine (3a): Light-yellow solid (2.05 g, 91%). Mp 149–151 °C. IR (KBr) cm^{-1}: 1353, 1534 (NO_2), 1617 (C=N). GC-MS m/z = 225 [M$^+$]. Anal. Calcd for $C_{15}H_{15}NO$: C, 79.97; H, 6.71; N, 6.22%. Found: C, 80.08; H, 6.84; N, 6.15%.

4-Ethoxyphenyl-*N*-(4-nitrobenzylidene)amine (3b): Yellow crystal (2.62 g, 97%). Mp 124–126 °C. IR (KBr) cm^{-1}: 1353, 1536 (NO_2), 1620 (C=N). ^{1}H NMR ($CDCl_3$): δ 1.33 (Me, t, 3H, J = 7.0 Hz), 3.88 (OCH_2, q, 2H, J = 7.0 Hz), 6.81–8.18 (ArH, m, 8H), 8.44 (HC=N, s, 1H). ^{13}C NMR ($CDCl_3$): δ 14.8 (Me), 63.7 (OCH_2), 115.1–154.5 (aromatic carbons), 158.7 (C=N). GC-MS m/z = 270 [M$^+$]. Anal. Calcd for $C_{15}H_{14}N_2O_3$: C, 66.66; H, 5.22; N, 10.36%. Found: C, 66.62; H, 5.39; N, 10.32%.

***N*-(4-Chlorobenzylidene)-4-ethoxyphenylamine (3c):** Milky-colored solid (2.43 g, 94%). Mp 92–94 °C. IR (KBr) cm^{-1}: 1620 (C=N). ^{1}H NMR ($CDCl_3$): δ 1.43 (Me, t, 3H, J = 7.0 Hz), 4.00 (OCH_2, q, 2H, J = 7.0 Hz), 6.87–7.80 (ArH, m, 8H), 8.39 (HC=N, s, 1H). ^{13}C NMR ($CDCl_3$): δ 14.8 (Me), 63.6 (OCH_2), 114.9–156.4 (aromatic carbons), 157.9 (C=N). GC-MS m/z = 261 [M$^+$, ^{37}Cl], 259 [M$^+$, ^{35}Cl]. Anal. Calcd for $C_{15}H_{14}ClNO$: C, 69.36; H, 5.43; N, 5.39%. Found: C, 69.29; H, 5.49; N, 5.44%.

4-Ethoxyphenyl-*N*-(4-methoxybenzylidene)amine (3d): Milky-colored solid (2.42 g, 95%). Mp 128–130 °C. IR (KBr) cm^{-1}: 1612 (C=N). ^{1}H NMR ($CDCl_3$): δ 1.41 (Me, t, 3H, J = 7.0 Hz), 3.86 (OMe, s, 3H), 4.03 (OCH_2, q, 2H, J = 7.0 Hz), 6.88–7.83 (ArH, m, 8H), 8.39 (HC=N, s, 1H). ^{13}C NMR ($CDCl_3$): δ 14.9 (Me), 55.4 (OMe), 63.6 (OCH_2), 114.1–157.7 (aromatic carbons), 161.9 (C=N). GC-MS m/z = 255 [M$^+$]. Anal. Calcd for $C_{16}H_{17}NO_2$: C, 75.27; H, 6.71; N, 5.49%. Found: C, 75.17; H, 6.80; N, 5.45%.

(4-Methoxybenzylidene)aniline (3e): Yellow solid (1.90 g, 90%). Mp 60–62 °C. IR (KBr) cm^{-1}: 1621 (C=N). GC-MS m/z = 211 [M$^+$]. Anal. Calcd for $C_{14}H_{13}NO$: C, 79.59; H, 6.20; N, 6.63%. Found: C, 79.48; H, 6.33; N, 6.56%.

Benzylideneaniline (3f): Light yellow solid (1.56 g, 86%). Mp 40–42 °C. IR (KBr) cm^{-1}: 1624 (C=N). GC-MS m/z = 181 [M$^+$]. Anal. Calcd for $C_{13}H_{11}N$: C, 86.15; H, 6.12; N, 7.73%. Found: C, 86.24; H, 6.29; N, 7.63%.

***N*-(4-Methoxybenzylidene)-4-methoxyphenylamine (3g):** Gray solid (2.14 g, 89%). Mp 137–139 °C. IR (KBr) cm^{-1}: 1620 (C=N). GC-MS m/z = 241 [M$^+$]. Anal. Calcd for

$C_{15}H_{15}NO_2$: C, 74.67; H, 6.27; N, 5.81%. Found: C, 74.75; H, 6.40; N, 5.92%.

***N*-(4-Nitrobenzylidene)phenylmethanamine (3h):** Orange solid (2.06 g, 86%). Mp 55–57 °C. IR (KBr) cm^{-1}: 1337, 1511 (NO_2), 1623 (C=N). GC-MS $m/z = 240$ [M^+]. Anal. Calcd for $C_{14}H_{12}N_2O_2$: C, 69.99; H, 5.03; N, 11.66%. Found: C, 70.09; H, 5.18; N, 11.78%.

***N*-(4-Chlorobenzylidene)-4-(phenyldiazenyl)aniline (3i):** Orange solid (2.69 g, 84%). Mp 156–158 °C. IR (KBr) cm^{-1}: 1609 (C=N). GC-MS $m/z = 321$ [M^+, ^{37}Cl], 319 [M^+, ^{35}Cl]. Anal. Calcd for $C_{19}H_{14}ClN_3$: C, 71.36; H, 4.41; N, 13.14%. Found: C, 71.45; H, 4.60; N, 13.03%.

General Procedure for the Solid-Phase Polymer-Supported Synthesis of β-Lactams 5a–5i. Polymer-supported phthaloylglycine **2** (1.0 g, 0.9 mmol g^{-1}, theoretical load) was swollen in dry CH_2Cl_2 (15 mL) and the corresponding imine (3.6 mmol), chloromethylenedimethylammonium chloride (**4**) (5.4 mmol), and triethylamine (9.0 mmol) were added at room temperature. The mixture was stirred overnight at room temperature and the filtered resin was washed with H_2O (2 × 10 mL), DMF (2 × 10 mL), EtOH (2 × 10 mL), and CH_2Cl_2 (2 × 10 mL) and dried in vacuo to provide Merrifield resin-bound β-lactams **5a–5i**.

General Procedure for the Cleavage of β-Lactams 5 from Merrifield Resin. With trifluoroacetic acid (TFA): Merrifield resin-bound β-lactams **5a–5i** (0.5 mmol) were treated at room temperature with 10% TFA in CH_2Cl_2 (5 mL) for 1 h. The mixture was filtered, washed with CH_2Cl_2 (2 × 8 mL) and then with H_2O (10 mL). The organic phase was dried and evaporated under reduced pressure to give 4-carboxyphthalimido-β-lactams **6a–6i**.

With aluminum chloride ($AlCl_3$): Merrifield resin-bound β-lactams **5a–5i** (0.5 mmol) were swollen in CH_2Cl_2 (4 mL) for 30 min at room temperature. After cooling to 0 °C, aluminum chloride (0.27 g, 2.0 mmol) was added and the mixture was stirred for 30 min at the same temperature. The resin was filtered and washed with EtOAc (2 × 3 mL). The filtrate was transferred to a separatory funnel, washed with 0.5 M HCl (5 mL) and aqueous layers were extracted with EtOAc (1 × 3 mL). The combined extracts were dried and evaporated to give 4-carboxyphthalimido-β-lactams **6a–6i**.

With methylhydrazine ($MeNHNH_2$): To the pre-swollen polymer-supported β-lactams **5a–5i** (0.5 mmol) in dry CH_2Cl_2 (5 mL) methylhydrazine (0.04 mL, 0.7 mmol) was added and the reaction mixture was stirred at room temperature for 32 h. The resin was filtered and washed with CH_2Cl_2 (2 × 5 mL). The filtrate was washed with H_2O (10 mL), saturated $NaHCO_3$ (10 mL), dried over anhydrous Na_2SO_4, and evaporated to give 3-amino-β-lactams **8a–8i**.

2-[1-(4-Ethoxyphenyl)-2-oxo-4-*p*-tolylazetidin-3-yl]-1,3-dioxoisoindoline-5-carboxylic Acid (6a): White solid (0.16 g, 68%). Mp >230 °C. IR (KBr) cm^{-1}: 1346, 1523 (NO_2), 1712 (CO, COOH), 1732, 1769 (CO, phth), 1779 (CO, β-lactam), 2850–3460 (OH). ^1H NMR (DMSO-d_6): δ 1.26 (Me, t, 3H, $J = 7.0$ Hz), 2.44 (Me, s, 3H), 4.08 (OCH_2, q, 2H, $J = 7.0$ Hz), 5.18 (H-4, d, 1H, $J = 2.3$ Hz), 5.56 (H-3, d, 1H, $J = 2.3$ Hz), 6.68–7.84 (ArH, m, 11H), 13.34 (COOH, brs, 1H). ^{13}C NMR (DMSO-d_6): δ 15.3 (Me), 21.7 (Me), 60.2 (OCH_2), 61.8 (C-4), 63.3 (C-3), 113.0–157.1 (aromatic carbons), 162.5 (CO, phth), 165.3 (CO, β-lactam), 174.7 (CO, COOH). GC-MS $m/z = 470$ [M^+]. Anal. Calcd for $C_{27}H_{22}N_2O_6$: C, 68.93; H, 4.71; N, 5.95%. Found: C, 69.06; H, 4.84; N, 5.88%.

2-[1-(4-Ethoxyphenyl)-2-(4-nitrophenyl)-4-oxoazetidin-3-yl]-1,3-dioxoisoindoline-5-carboxylic Acid (6b): Pale yellow solid (0.18 g, 71%). Mp >230 °C. IR (KBr) cm^{-1}: 1346, 1523 (NO_2), 1718 (CO, COOH), 1736, 1771 (CO, phth), 1780 (CO, β-lactam), 2903–3530 (OH). ^1H NMR (DMSO-d_6): δ 1.30 (Me, t, 3H, $J = 6.9$ Hz), 3.99 (OCH_2, q, 2H, $J = 6.9$ Hz), 5.23 (H-4, d, 1H, $J = 2.5$ Hz), 5.59 (H-3, d, 1H, $J = 2.5$ Hz), 6.80–7.85 (ArH, m, 11H), 13.41 (COOH, brs, 1H). ^{13}C NMR (DMSO-d_6): δ 15.4 (Me), 59.1 (OCH_2), 61.0 (C-4), 64.6 (C-3), 114.3–156.7 (aromatic carbons), 161.1 (CO, phth), 165.8 (CO, β-lactam), 173.1 (CO, COOH). GC-MS $m/z = 501$ [M^+]. Anal. Calcd for $C_{26}H_{19}N_3O_8$: C, 62.28; H, 3.82; N, 8.38%. Found: C, 62.16; H, 3.88; N, 8.43%.

2-[2-(4-Chlorophenyl)-1-(4-ethoxyphenyl)-4-oxoazetidin-3-yl]-1,3-dioxoisoindoline-5-carboxylic Acid (6c): White solid (0.16 g, 66%). Mp >230 °C. IR (KBr) cm^{-1}: 1711 (CO, COOH), 1730, 1767 (CO, phth), 1776 (CO, β-lactam), 2820–3508 (OH). ^1H NMR (DMSO-d_6): δ 1.37 (Me, t, 3H, $J =$ 6.9 Hz), 3.91 (OCH_2, q, 2H, $J = 6.9$ Hz), 5.16 (H-4, d, 1H, $J = 2.5$ Hz), 5.30 (H-3, d, 1H, $J = 2.5$ Hz), 6.67–8.01 (ArH, m, 11H), 13.29 (COOH, brs, 1H). ^{13}C NMR (DMSO-d_6): δ 14.5 (Me), 61.7 (OCH_2), 62.6 (C-4), 64.3 (C-3), 117.8–157.3 (aromatic carbons), 160.9 (CO, phth), 166.4 (CO, β-lactam), 175.0 (CO, COOH). GC-MS $m/z = 492$ [M^+, ^{37}Cl], 490 [M^+, ^{35}Cl]. Anal. Calcd for $C_{26}H_{19}ClN_2O_6$: C, 63.61; H, 3.90; N, 5.71%. Found: C, 63.70; H, 4.02; N, 5.78%.

2-[1-(4-Ethoxyphenyl)-2-(4-methoxyphenyl)-4-oxoazetidin-3-yl]-1,3-dioxoisoindoline-5-carboxylic Acid (6d): White solid (0.19 g, 78%). Mp >230 °C. IR (KBr) cm^{-1}: 1724 (CO, COOH), 1736, 1770 (CO, phth), 1782 (CO, β-lactam), 2875–3618 (OH). ^1H NMR (DMSO-d_6): δ 1.27 (Me, t, 3H, $J = 7.0$ Hz), 3.63 (OMe, s, 3H), 3.75 (OCH_2, q, 2H, $J = 7.0$ Hz), 4.91 (H-4, d, 1H, $J = 2.4$ Hz), 5.25 (H-3, d, 1H, $J = 2.4$ Hz), 6.74–7.96 (ArH, m, 11H), 13.11 (COOH, brs, 1H). ^{13}C NMR (DMSO-d_6): δ 15.1 (Me), 56.3 (OMe), 60.0 (OCH_2), 62.4 (C-4), 63.8 (C-3), 114.8–159.5 (aromatic carbons), 162.2 (CO, phth), 167.1 (CO, β-lactam), 173.7 (CO, COOH). GC-MS $m/z = 486$ [M^+]. Anal. Calcd for $C_{27}H_{22}N_2O_7$: C, 66.66; H, 4.56; N, 5.76%. Found: C, 66.58; H, 4.67; N, 5.64%.

2-[2-(4-Methoxyphenyl)-4-oxo-1-phenylazetidin-3-yl]-1,3-dioxoisoindoline-5-carboxylic Acid (6e): White solid (0.16 g, 73%). Mp >230 °C. IR (KBr) cm^{-1}: 1719 (CO, COOH), 1729, 1761 (CO, phth), 1774 (CO, β-lactam), 2850–3410 (OH). ^1H NMR (DMSO-d_6): δ 3.76 (OMe, s, 3H), 5.26 (H-4, d, 1H, $J = 2.6$ Hz), 5.36 (H-3, d, 1H, $J = 2.6$ Hz), 6.86–7.82 (ArH, m, 12H), 13.19 (COOH, brs, 1H). ^{13}C NMR (DMSO-d_6): δ 55.3 (OMe), 60.8 (C-4), 62.8 (C-3), 114.8–160.1 (aromatic carbons), 162.2 (CO, phth), 166.8 (CO, β-lactam), 172.5 (CO, COOH). GC-MS $m/z = 442$ [M^+]. Anal. Calcd for $C_{25}H_{18}N_2O_6$: C, 67.87; H, 4.10; N, 6.33%. Found: C, 67.95; H, 4.23; N, 6.40%.

1,3-Dioxo-2-(2-oxo-1,4-diphenylazetidin-3-yl)isoindoline-5-carboxylic Acid (6f): White solid (0.13 g, 64%). Mp >230 °C. IR (KBr) cm^{-1}: 1722 (CO, COOH), 1731, 1767 (CO, phth), 1776 (CO, β-lactam), 2980–3636 (OH). ^1H NMR

(DMSO-d_6): δ 5.29 (H-4, d, 1H, $J = 2.6$ Hz), 5.38 (H-3, d, 1H, $J = 2.6$ Hz), 6.90–7.86 (ArH, m, 13H), 13.26 (COOH, brs, 1H). ^{13}C NMR (DMSO-d_6): δ 61.2 (C-4), 62.7 (C-3), 117.6–137.1 (aromatic carbons), 162.0 (CO, phth), 166.8 (CO, β-lactam), 173.8 (CO, COOH). GC-MS $m/z = 412$ [M^+]. Anal. Calcd for $C_{24}H_{16}N_2O_5$: C, 69.90; H, 3.91; N, 6.79%. Found: C, 69.79; H, 4.03; N, 6.71%.

2-[1,2-Bis(4-methoxyphenyl)-4-oxoazetidin-3-yl]-1,3-dioxoisoindoline-5-carboxylic Acid (6g): White solid (0.18 g, 75%). Mp >230 °C. IR (KBr) cm^{-1}: 1727 (CO, COOH), 1733, 1765 (CO, phth), 1779 (CO, β-lactam), 2764–3390 (OH). ^{1}H NMR (DMSO-d_6): δ 3.74, 3.80 (2 × OMe, s, 6H), 5.26 (H-4, d, 1H, $J = 2.4$ Hz), 5.30 (H-3, d, 1H, $J = 2.4$ Hz), 6.49–7.85 (ArH, m, 11H), 13.36 (COOH, brs, 1H). ^{13}C NMR (DMSO-d_6): δ 55.3, 55.3 (2 × OMe), 61.1 (C-4), 62.8 (C-3), 114.3–160.2 (aromatic carbons), 161.7 (CO, phth), 166.9 (CO, β-lactam), 173.4 (CO, COOH). GC-MS $m/z = 472$ [M^+]. Anal. Calcd for $C_{26}H_{20}N_2O_7$: C, 66.10; H, 4.27; N, 5.93%. Found: C, 66.19; H, 4.40; N, 5.85%.

2-[1-Benzyl-2-(4-nitrophenyl)-4-oxoazetidin-3-yl]-1,3-dioxoisoindoline-5-carboxylic Acid (6h): White solid (0.17 g, 72%). Mp >230 °C. IR (KBr) cm^{-1}: 1350, 1536 (NO_2), 1717 (CO, COOH), 1722, 1761 (CO, phth), 1775 (CO, β-lactam), 2845–3565 (OH). ^{1}H NMR (DMSO-d_6): δ 4.33, 5.02 (CH_2-benzyl, d, 2H, $J = 14.9$ Hz), 5.04 (H-4, d, 1H, $J = 2.4$ Hz), 5.63 (H-3, d, 1H, $J = 2.4$ Hz), 7.27–8.34 (ArH, m, 12H), 13.24 (COOH, brs, 1H). ^{13}C NMR (DMSO-d_6): δ 46.0 (CH_2), 59.8 (C-4), 60.3 (C-3), 123.0–147.7 (aromatic carbons), 163.5 (CO, phth), 166.6 (CO, β-lactam), 174.8 (CO, COOH). GC-MS $m/z = 471$ [M^+]. Anal. Calcd for $C_{25}H_{17}N_3O_7$: C, 63.69; H, 3.63; N, 8.91%. Found: C, 63.62; H, 3.75; N, 8.94%.

2-{2-(4-Chlorophenyl)-4-oxo-1-[4-(phenyldiazenyl)phenyl]azetidin-3-yl}-1,3-dioxoisoindoline-5-carboxylic Acid (6i): Orange-red solid (0.19 g, 70%). Mp >230 °C. IR (KBr) cm^{-1}: 1729 (CO, COOH), 1737, 1768 (CO, phth), 1781 (CO, β-lactam), 2820–3538 (OH). ^{1}H NMR (DMSO-d_6): δ 5.31 (H-4, d, 1H, $J = 1.6$ Hz), 5.44 (H-3, d, 1H, $J = 1.6$ Hz), 7.20–7.89 (ArH, m, 16H), 13.37 (COOH, brs, 1H). ^{13}C NMR (DMSO-d_6): δ 60.9 (C-4), 62.9 (C-3), 117.9–152.6 (aromatic carbons), 162.0 (CO, phth), 166.7 (CO, β-lactam), 173.9 (CO, COOH). GC-MS $m/z = 552$ [M^+, ^{37}Cl], 550 [M^+, ^{35}Cl]. Anal. Calcd for $C_{30}H_{19}ClN_4O_5$: C, 65.40; H, 3.48; N, 10.17%. Found: C, 65.32; H, 3.61; N, 10.05%.

3-Amino-1-(4-ethoxyphenyl)-4-*p*-tolylazetidin-2-one (8a): White solid (0.09 g, 58%). Mp 123–125 °C. IR (KBr) cm^{-1}: 1765 (CO, β-lactam), 3350, 3395 (NH_2). ^{1}H NMR ($CDCl_3$): δ 1.25 (Me, t, 3H, $J = 6.8$ Hz), 2.02 (NH_2, brs, 2H), 2.23 (Me, s, 3H), 3.81 (OCH_2, q, 2H, $J = 6.8$ Hz), 3.87 (H-4, d, 1H, $J = 1.9$ Hz), 4.47 (H-3, d, 1H, $J = 1.9$ Hz), 6.62–7.17 (ArH, m, 8H). ^{13}C NMR ($CDCl_3$): δ 14.0 (Me), 20.1 (Me), 62.8 (OCH_2), 65.4 (C-4), 68.9 (C-3), 113.2–154.4 (aromatic carbons), 166.5 (CO, β-lactam). GC-MS $m/z = 296$ [M^+]. Anal. Calcd for $C_{18}H_{20}N_2O_2$: C, 72.95; H, 6.80; N, 9.45%. Found: C, 73.08; H, 6.93; N, 9.36%.

3-Amino-1-(4-ethoxyphenyl)-4-(4-nitrophenyl)azetidin-2-one (8b): White solid (0.10 g, 61%). Mp 141–143 °C. IR (KBr) cm^{-1}: 1343, 1528 (NO_2), 1763 (CO, β-lactam), 3362, 3409 (NH_2). ^{1}H NMR ($CDCl_3$): δ 1.31 (Me, t, 3H, $J = 7.2$ Hz), 2.02 (NH_2, brs, 2H), 3.95 (OCH_2, q, 2H, $J = 7.2$ Hz), 4.03 (H-4, d, 1H, $J = 2.1$ Hz), 4.70 (H-3, d, 1H, $J = 2.1$ Hz), 6.46–8.18 (ArH, m, 8H). ^{13}C NMR ($CDCl_3$): δ 14.9 (Me), 63.9 (OCH_2), 69.4 (C-4), 70.3 (C-3), 114.7–155.8 (aromatic carbons), 166.9 (CO, β-lactam). GC-MS $m/z = 327$ [M^+]. Anal. Calcd for $C_{17}H_{17}N_3O_4$: C, 62.38; H, 5.23; N, 12.84%. Found: C, 62.31; H, 5.34; N, 12.76%.

3-Amino-4-(4-chlorophenyl)-1-(4-ethoxyphenyl)azetidin-2-one (8c): White solid (0.08 g, 53%). Mp 122–124 °C. IR (KBr) cm^{-1}: 1760 (CO, β-lactam), 3349, 3391 (NH_2). ^{1}H NMR ($CDCl_3$): δ 1.35 (Me, t, 3H, $J = 7.0$ Hz), 2.09 (NH_2, brs, 2H), 3.90 (OCH_2, q, 2H, $J = 7.0$ Hz), 3.95 (H-4, d, 1H, $J = 1.9$ Hz), 4.59 (H-3, d, 1H, $J = 1.9$ Hz), 6.73–7.37 (ArH, m, 8H). ^{13}C NMR ($CDCl_3$): δ 15.0 (Me), 63.9 (OCH_2), 65.9 (C-4), 70.0 (C-3), 114.5–155.6 (aromatic carbons), 167.3 (CO, β-lactam). GC-MS $m/z = 318$ [M^+, ^{37}Cl], 316 [M^+, ^{35}Cl]. Anal. Calcd for $C_{17}H_{17}ClN_2O_2$: C, 64.46; H, 5.41; N, 8.84%. Found: C, 64.55; H, 5.58; N, 8.91%.

3-Amino-1-(4-ethoxyphenyl)-4-(4-methoxyphenyl)azetidin-2-one (8d): White solid (0.09 g, 56%). Mp 116–118 °C. IR (KBr) cm^{-1}: 1762 (CO, β-lactam), 3351, 3397 (NH_2). ^{1}H NMR ($CDCl_3$): δ 1.37 (Me, t, 3H, $J = 6.9$ Hz), 2.52 (NH_2, brs, 2H), 3.79 (OMe, s, 3H), 3.94 (OCH_2, q, 2H, $J = 6.9$ Hz), 3.97 (H-4, d, 1H, $J = 2.0$ Hz), 4.56 (H-3, d, 1H, $J = 2.0$ Hz), 6.72–7.25 (ArH, m, 8H). ^{13}C NMR ($CDCl_3$): δ 14.8 (Me), 55.3 (OMe), 63.8 (OCH_2), 66.2 (C-4), 69.8 (C-3), 113.4–159.7 (aromatic carbons), 167.6 (CO, β-lactam). GC-MS $m/z = 312$ [M^+]. Anal. Calcd for $C_{18}H_{20}N_2O_3$: C, 69.21; H, 6.45; N, 8.97%. Found: C, 69.29; H, 6.57; N, 8.89%.

3-Amino-4-(4-methoxyphenyl)-1-phenylazetidin-2-one (8e): White solid (0.08 g, 58%). Mp 129–131 °C. IR (KBr) cm^{-1}: 1758 (CO, β-lactam), 3338, 3391 (NH_2). ^{1}H NMR ($CDCl_3$): δ 2.17 (NH_2, brs, 2H), 3.71 (OMe, s, 3H), 3.92 (H-4, d, 1H, $J = 1.9$ Hz), 4.54 (H-3, d, 1H, $J = 1.9$ Hz), 6.54–7.27 (ArH, m, 9H). ^{13}C NMR ($CDCl_3$): δ 55.1 (OMe), 66.1 (C-4), 69.9 (C-3), 113.3–159.6 (aromatic carbons), 168.4 (CO, β-lactam). GC-MS $m/z = 268$ [M^+]. Anal. Calcd for $C_{16}H_{16}N_2O_2$: C, 71.62; H, 6.01; N, 10.44%. Found: C, 71.53; H, 6.17; N, 10.36%.

3-Amino-1,4-diphenylazetidin-2-one (8f): White solid (0.06 g, 50%). Mp 154–156 °C. IR (KBr) cm^{-1}: 1767 (CO, β-lactam), 3348, 3401 (NH_2). ^{1}H NMR ($CDCl_3$): δ 2.40 (NH_2, brs, 2H), 3.97 (H-4, d, 1H, $J = 2.0$ Hz), 4.61 (H-3, d, 1H, $J = 2.0$ Hz), 6.55–7.33 (ArH, m, 10H). ^{13}C NMR ($CDCl_3$): δ 66.5 (C-4), 69.9 (C-3), 113.4–146.8 (aromatic carbons), 168.3 (CO, β-lactam). GC-MS $m/z = 238$ [M^+]. Anal. Calcd for $C_{15}H_{14}N_2O$: C, 75.61; H, 5.92; N, 11.76%. Found: C, 75.50; H, 6.08; N, 11.63%.

3-Amino-1,4-bis(4-methoxyphenyl)azetidin-2-one (8g): White solid (0.08 g, 51%). Mp 131–133 °C. IR (KBr) cm^{-1}: 1761 (CO, β-lactam), 3353, 3409 (NH_2). ^{1}H NMR ($CDCl_3$): δ 2.03 (NH_2, brs, 2H), 3.60, 3.65 (2 × OMe, s, 6H), 3.86 (H-4, d, 1H, $J = 2.2$ Hz), 4.46 (H-3, d, 1H, $J = 2.2$ Hz), 6.61–7.13 (ArH, m, 8H). ^{13}C NMR ($CDCl_3$): δ 54.3, 54.6 (2 × OMe), 65.2 (C-4), 68.9 (C-3), 112.3–158.7 (aromatic carbons), 166.7 (CO, β-lactam). GC-MS $m/z = 298$ [M^+]. Anal. Calcd for $C_{17}H_{18}N_2O_3$: C, 68.44; H, 6.08; N, 9.39%. Found: C, 68.52; H, 6.21; N, 9.46%.

3-Amino-1-benzyl-4-(4-nitrophenyl)azetidin-2-one (8h): White solid (0.08 g, 55%). Mp 90–92 °C. IR (KBr) cm^{-1}: 1348, 1522 (NO_2), 1766 (CO, β-lactam), 3340, 3388 (NH_2).

^{1}H NMR ($CDCl_3$): δ 1.83 (NH_2, brs, 2H), 4.02, 4.84 (CH_2-benzyl, d, 2H, $J = 14.8$ Hz), 4.58 (H-4, d, 1H, $J = 2.4$ Hz), 4.76 (H-3, d, 1H, $J = 2.4$ Hz), 7.13–8.24 (ArH, m, 9H). ^{13}C NMR ($CDCl_3$): δ 44.8 (CH_2), 61.6 (C-4), 65.3 (C-3), 123.7–147.8 (aromatic carbons), 170.0 (CO, β-lactam); GC-MS $m/z = 297$ [M^+]. Anal. Calcd for $C_{16}H_{15}N_3O_3$: C, 64.64; H, 5.09; N, 14.13%. Found: C, 64.75; H, 5.18; N, 14.06%.

3-Amino-4-(4-chlorophenyl)-1-[4-(phenyldiazenyl)phenyl]-azetidin-2-one (8i): Orange solid (0.10 g, 53%). Mp 164–166 °C. IR (KBr) cm^{-1}: 1765 (CO, β-lactam), 3342, 3381 (NH_2). ^{1}H NMR ($CDCl_3$): δ 2.18 (NH_2, brs, 2H), 4.81 (H-4, d, 1H, $J = 2.2$ Hz), 4.89 (H-3, d, 1H, $J = 2.2$ Hz), 6.55–7.81 (ArH, m, 13H). ^{13}C NMR ($CDCl_3$): δ 60.1 (C-4), 60.4 (C-3), 112.5–153.0 (aromatic carbons), 174.7 (CO, β-lactam). GC-MS $m/z = 378$ [M^+, ^{37}Cl], 376 [M^+, ^{35}Cl]. Anal. Calcd for $C_{21}H_{17}ClN_4O$: C, 66.93; H, 4.55; N, 14.87%. Found: C, 70.08; H, 4.67; N, 14.93%.

General Method for Regeneration of Polymer-Supported Trimellitic Anhydride 1. The resulting hydroxymethyl resin **7** (1.0 g, 1.2 mmol g^{-1}, theoretical load) was suspended in CH_2Cl_2 (15 mL) and stirred with trimellitic anhydride (0.9 g, 4.8 mmol), dicyclohexylcarbodiimide (DCC) (1.5 g, 7.5 mmol), and catalytic 4-dimethylaminopyridine (DMAP) for 8 h. The reaction mixture was then filtered, washed with DMF (3 × 10), EtOH (3 × 10), and CH_2Cl_2 (3 × 10), and dried.

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