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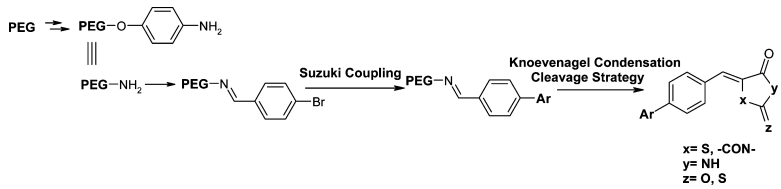

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Articles

Soluble Polymer-Supported Synthesis of 5-Arylidene Thiazolidinones and Pyrimidinones Using a Novel Traceless Linker Strategy

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An efficient method for the soluble polymer-supported synthesis of 5-arylidene thiazolidinones and pyrimidinones using aniline as a traceless linker was described. Aldehyde substrates were attached to the polyethylene glycol (PEG)-bound aniline via an imine linkage, and after the subsequent PEG-promoted Suzuki coupling reaction for the diversification, Knoevenagel condensation was readily employed as the cleavage strategy.

Introduction

Polymer-supported synthesis has emerged as a powerful technique for the generation of structurally diverse compounds in the drug discovery community. An important aspect to applying this technique is the choice of suitable support.[1] In last two decades, insoluble polymer-supported organic reactions were dramatically developed to synthesize small molecules, since they can easily be isolated by filtration and purified conveniently.[2] But the insoluble polymer supports also exhibit some disadvantages, including heterogeneous reaction conditions and the difficulty to characterize the intermediates. In an attempt to overcome these problems, soluble polymer supports like polyethylene glycol (PEG) have been investigated.[3,4] The PEG support enables the use of homogeneous reaction conditions and the standard analytical techniques for reaction monitoring. Moreover, it is also inexpensive and readily available.

5-Arylidene thiazolidinone and pyrimidinone moieties are important structure elements in medicinal chemistry and they show a broad spectrum of biological activities.[5] Therefore, facile preparation of various 5-arylidene thiazolidinones and pyrimidinones for lead discovery is highly desirable. Some methods were developed for the polymer supported synthesis of these useful scaffolds.[6] Those methods, however, are "nontraceless" and have the drawback of either inconvenient attachment or cumbersome cleavage. Moreover, to the best of our knowledge, synthesis of 5-arylidene thiazolidinone or pyrimidinone compounds on soluble polymer supports has also not been demonstrated.

Herein, we would like to present an efficient method for the preparation of 5-arylidene thiazolidinones and pyrimidinones on PEG support with aniline as a novel traceless linker. Followed by the attachment of aldehyde substrates to the PEG-bound aniline via an imine linkage and subsequent PEG-supported Suzuki reaction for diversification, corresponding 5-arylidene thiazolidinone or pyrimidinone products were readily afforded in good yield with high purity, using Knoevenagel condensation as a cleavage strategy.

Results and Discussion

The 4-hydroxyaniline linker was assembled on the PEG4000 in three steps (Scheme 1).[7] 4-Nitrophenol was O-alkylated with mesylated PEG in the K_2CO_3−acetone system and then hydrogenated with Pd/C−H_2 in MeOH to give polymer **3**, which was characterized by ^{1}H NMR and FT-IR.

Our loading and cleavage strategy was investigated on the polymer **3** (Scheme 2). Various aldehydes were attached to polymer **3** via imine linkage in hot methanol to afford PEG-bound imines **4a**−**d** which were confirmed by the appearance of the single peak of the imine proton in the ^{1}H NMR spectrum. Since the imine bond is an ideal substrate for Knoevenagel condensation,[8] polymer **4a**−**d** could be cleaved efficiently by thiazolidine-2, 4-dione **8**{*1*} in AcOH under Knoevenagel reaction conditions to give the thiazolidinone products **5a**−**d**, which were simply precipitated from water and filtrated without any further purification to afford high purities with excellent yields (Table 1).[9]

As described in previous publications,[10] imine linkage would be stable to a range of reaction conditions, and the

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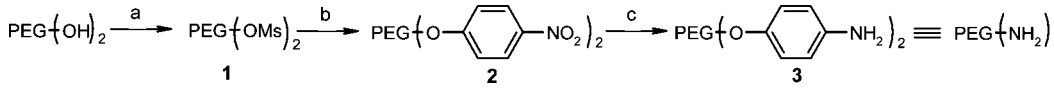
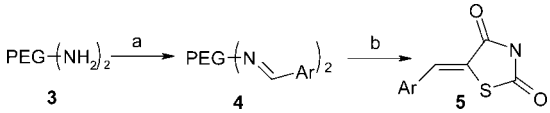
Scheme 1. Preparation of Polymer-Bound Aniline[a]



[a] Reagents and conditions: (a) MsCl, DCM, rt, overnight; (b) 4-nitrophenol, K_2CO_3, acetone, reflux, 12 h; (c) Pd/C, H_2, rt, 5 h.

Scheme 2. Investigation of Loading and Cleavage Strategy on Polymer **3**[a]



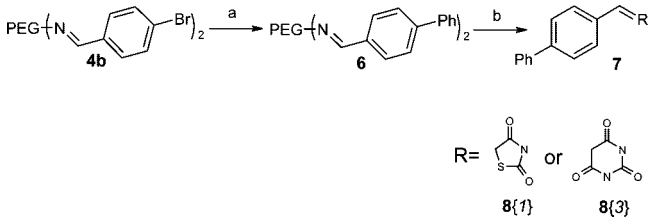
[a] Reagents and conditions: (a) 3 equiv Ar-CHO, MeOH, 50 °C, 6 h; (b) 3 equiv thiazolidine-2,4-dione **8**{*1*}, AcOH, NaOAc, 120 °C, 12 h.

Table 1. Cleavage of Polymer **4b** with Thiazolidine-2,4-dione **8**{*1*}

product	Ar	yield (%)[a]	purity (%)[b]
5a	phenyl	96	100
5b	4-bromophenyl	92	100
5c	4-hydroxyphenyl	91	100
5d	2-naphthyl	91	100

[a] Overall isolated yield based on the initial loading of the polymer. [b] Purity determined by HPLC analysis (UV detection at $\lambda = 254$ and 214 nm) without any further purification.

Scheme 3. Suzuki Coupling of Polymer **4b**[a]



[a] Reagents and conditions: (a) 2.4 equiv phenylboronic acid, 1 mol % $Pd(OAc)_2$, K_2CO_3, MeOH, 80°C, 8 h; (b) 3 equiv thiazolidine-2,4-dione **8**{*1*}or pyrimidine-2,4,6-trione **8**{*3*}, AcOH, NaOAc, 120 °C, 12 h.

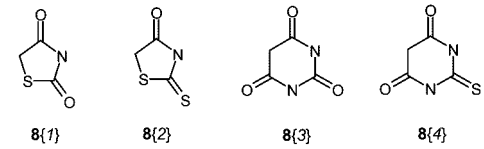
effort to develop the diversity of the library was made. When an appropriately substituted aldehyde was attached to the PEG support, the diversity of the compound could be increased by further PEG-supported reaction. The 5-biarylidene thiazolidine-2,4-diones have shown inhibitory activity against protein tyrosine phosphatase,[5c] and therefore, we performed palladium-catalyzed coupling reactions with PEG-bound intermediate polymer **4b** for the diversification (Scheme 3). Suzuki coupling of PEG-bound aryl halide has been demonstrated to be efficient, since PEG works not only as the carrier but also as the phase-transfer catalyst (PTC).[11] Palladium acetate, carbonate base, and aqueous solvent have been commonly applied for the PEG-supported ligandless Suzuki reaction. Considering the lability of the imine linkage to water, we employed methanol as solvent in our investigation.[12] In the presence of catalytic amount of Pd $(OAc)_2$ (1 mol %), phenylboronic acid was smoothly reacted with polymer **4b** under 80 °C in sealed vial, and followed by general precipitation, filtration, and washing workup, PEG-bound biaryl intermediate polymer **6** were afforded. Finally the products **7a** and **7b** were obtained from cleavage reaction of polymer **6** with thiazolidine-2,4-dione **8**{*1*} and pyrimidine-2,4,6-trione **8**{*3*} in excellent overall yield and purity (Table 2).

Table 2. Cleavage of Polymer **6** with **8**{*1*} and **8**{*3*}

product	R	yield (%)[a]	purity (%)[b]
7a	thiazolidine-2,4-dione	86	100
7b	pyrimidine-2,4,6-trione	92	100

[a] Overall isolated yield based on the initial loading of the polymer. [b] Purity determined by HPLC analysis (UV detection at $\lambda = 254$ and 214 nm) without any further purification.

Thiazolidinones and Pyrimidinones:



Arylboronic acids:

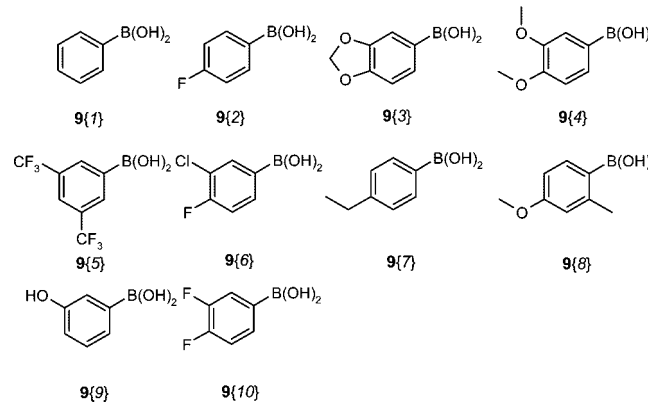
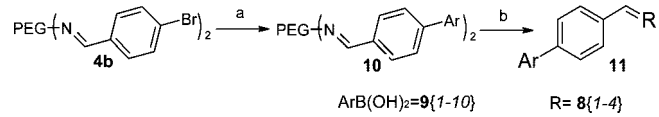


Figure 1. Diversity reagents.

Scheme 4. Preparation of the 5-Arylidene Thiazolidinones/ Pyrimidinones Library[a]



[a] Reagents and conditions: (a) 2.4 equiv Ar-$B(OH)_2$, 1 mol % $Pd(OAc)_2$, K_2CO_3, MeOH, 80 °C, 8 h; (b) 3 equiv R, AcOH, NaOAc, 120 °C, 12 h.

To evaluate the potential of such methodology for library production, PEG-bound intermediate polymer **4b** was coupled with ten substituted arylboronic acids **9**{*1*−*10*} (Figure 1) and then cleaved respectively by four commercial available thiazolidinones **8**{*1*−*2*} and pyrimidinones **8**{*3*−*4*} (Scheme 4). Only simple workup (precipitation, filtration, and washing) was needed after each reaction; and all the final products could be obtained in good yield with high purity (Table 3).

All compounds in this library were screened for inhibitors of protein tyrosine phosphatase 1B (PTP1B).[13] Some of them exhibited moderate inhibitory activity with IC_{50} values of $<10^{-5}$ M (Table 4). Comparing compounds **11**{*1*−*2, n*} with **11**{*3*−*4, n*}, the thiazolidinone scaffold appeared to be important in the PTP1B inhibitory activity and the introduction of the 3-chloro (**11**{*1*−*2, 6*}), 4-alkyl (**11**{*1*−*2, 7*}), 3-hydroxy (**11**{*1*−*2, 9*}), or 3,4-methylenedioxy (**11**{*1*−*2,*

Table 3. Library of 5-Arylidene Thiazolidinones/Pyrimidinones and Its Inhibition against PTP1B at a 5 μg/mL Concentration[13]

product	yield[a] (%)	purity[b] (%)	inhibition (%)	product	yield[a] (%)	purity[b] (%)	inhibition (%)
11{*1, 1*}	86	100	28	**11**{*3, 1*}	92	100	<20
11{*1, 2*}	84	96	22	**11**{*3, 2*}	89	100	<20
11{*1, 3*}	90	98	82	**11**{*3, 3*}	85	100	<20
11{*1, 4*}	85	100	<20	**11**{*3, 4*}	86	97	<20
11{*1, 5*}	85	100	30	**11**{*3, 5*}	90	96	<20
11{*1, 6*}	91	98	96	**11**{*3, 6*}	90	97	<20
11{*1, 7*}	82	99	77	**11**{*3, 7*}	85	100	<20
11{*1, 8*}	82	98	32	**11**{*3, 8*}	87	97	<20
11{*1, 9*}	79	98	60	**11**{*3, 9*}	80	96	<20
11{*1, 10*}	81	100	<20	**11**{*3, 10*}	91	92	<20
11{*2, 1*}	93	100	37	**11**{*4, 1*}	90	91	<20
11{*2, 2*}	83	99	<20	**11**{*4, 2*}	86	92	<20
11{*2, 3*}	84	96	83	**11**{*4, 3*}	87	96	<20
11{*2, 4*}	83	97	20	**11**{*4, 4*}	90	91	<20
11{*2, 5*}	81	99	<20	**11**{*4, 5*}	82	93	<20
11{*2, 6*}	87	91	62	**11**{*4, 6*}	88	93	29
11{*2, 7*}	80	95	91	**11**{*4, 7*}	83	95	30
11{*2, 8*}	88	97	40	**11**{*4, 8*}	80	92	<20
11{*2, 9*}	84	93	62	**11**{*4, 9*}	82	94	<20
11{*2, 10*}	84	98	<20	**11**{*4, 10*}	89	90	<20

[a] Overall isolated yield based on the initial loading of the polymer. [b] Purity determined by HPLC analysis (UV detection at $\lambda = 254$ and 214 nm) without any further purification.

Table 4. IC_{50} of Compounds **11**{*1−2, 3*}, **11**{*1−2, 6*}, **11**{*1−2, 7*}, and **11**{*1−2, 9*} against PTP1B

compound	IC_{50} (μM)	compound	IC_{50} (μM)
11{*1, 3*}	2.22 ± 0.12	**11**{*2, 3*}	3.64 ± 0.35
11{*1, 6*}	2.34 ± 0.09	**11**{*2, 6*}	4.77 ± 0.43
11{*1, 7*}	4.53 ± 0.36	**11**{*2, 7*}	3.75 ± 0.34
11{*1, 9*}	5.39 ± 0.72	**11**{*2, 9*}	5.75 ± 0.37

3}) substitution on the Ar moiety is generally more favored for the bioactivity.

Conclusions

We have developed an efficient method for the soluble polymer-supported synthesis of 5-arylidene thiazolidinone and pyrimidinone derivatives using PEG-bound aniline as traceless linker. Aldehyde substrates were attached to the polymer via an imine linkage and Suzuki coupling reactions were subsequently performed for the diversification. The thiazolidinone or pyrimidinone products were released from the PEG support conveniently in good yield with high purity. A library of 40 compounds was synthesized and screened against protein tyrosine phosphatase 1B. Several members of this library display moderate inhibitory activity. These findings encourage us to generate a further round of libraries for the discovery of novel PTP1B inhibitors to established inhibition pathways and generate new structure−activity relationships (SARs). The results will be reported in due course.

Experimental Section

IR spectra were recorded on Nicolet Magna-FTIR-750 spectrophotometer. The ^{1}H NMR (300 MHz) spectra were recorded on Varian Mercury-300 High Performance Digital FT-NMR with TMS as the internal standard, and ^{13}C NMR (100 MHz) spectra were determined with Varian Mercury-400 High Performance Digital FT-NMR. The ESI-MS were carried out on a Thermo Finnigan LCQDECAXP; the low-resolution EI-MS was measured on a MAT-95 spectrometer, and HREI-MS, on a MAT-77 spectrometer. Purity was recorded on Gilson high-performance liquid chromatography (HPLC) (306 pump, UV−vis-156 Detector, 215 liquid handle). TLC was carried out with glass precoated silica gel GF_{254} plates. Spots were visualized under UV light. All the solvents and reagents were used directly as obtained commercially unless otherwise noted.

General Method for the Preparation of PEG-Bound Aniline (3). PEG 4000 (10 g, 2.5 mmol) was dissolved in 150 mL DCM, and MsCl (1.3 mL, 15 mmol) was added dropwise. The reaction mixture was stirred at room temperature overnight and concentrated in vacuo. The crude product was dissolved in DCM and added dropwise with vigorous stirring to diethyl ether. The resulting precipitate was collected by filtration and washed with diethyl ether to give the polymer **1** as a white powder in quantitative yield (based on polymer recovery).

^{1}H NMR (300 MHz, $CDCl_3$): δ 4.38 (m, 4H, PEG-α-methylenes), 3.40−3.87 (bm, PEG), 3.08 (s, 6H).

To the suspension of the resulting PEG-bound mesylate and K_2CO_3 (1.04 g, 7.5 mmol) in 150 mL acetone was added the 4-nitrophenol (1.04 g, 7.5 mmol). The reaction mixture was maintained under reflux for 12 h. Upon filtration of the solids and solvent evaporation, the crude product was dissolved in DCM and added dropwise with vigorous stirring to diethyl ether. The resulting precipitate was collected by filtration and washed with isopropanol and diethyl ether to give the polymer **2** as bright yellow powder in 99% yield (based on polymer recovery).

^{1}H NMR (300 MHz, $CDCl_3$): δ 8.00 (d, $J = 9.5$ Hz, 4H), 6.61 (d, $J = 9.5$ Hz, 4H), 4.20 (m, 4H, PEG-α-methylenes), 3.37−3.85 (bm, PEG); FT-IR (KBr): 1510 cm^{-1}.

The obtained PEG-bound nitrobenzene was dissolved in 150 mL methanol, and 10 wt % Pd/C (1 g) was added under argon atmosphere at room temperature. After flushing the flask three times with vacuum/Ar cycles, a balloon filled with hydrogen gas was attached. The flask was evacuated again and filled with hydrogen gas. The reaction mixture was stirred at room temperature for 5 h. Upon filtration of the solids and solvent evaporation, the crude product was dissolved in DCM and added dropwise with vigorous stirring to diethyl ether. The resulting precipitate was collected by filtration and washed with diethyl ether to give the polymer **3** as brown powder in 96% yield (based on polymer recovery).

^{1}H NMR (300 MHz, $CDCl_3$): δ 6.58 (d, $J = 8.6$ Hz, 4H), 6.48 (d, $J = 8.6$ Hz, 4H), 4.06 (m, 4H, PEG-α-methylenes), 3.38−3.81 (bm, PEG); FT-IR (KBr): 3420, 3280 cm^{-1}.

General Method for the Preparation of Compounds 5a−5d. PEG-bound aniline (8.4 g, 2 mmol) and 4-bromobenzaldehyde (1.11 g, 6 mmol) were dissolved in 30 mL methanol. The reaction mixture was heated to 50 °C for 6 h and then concentrated in vacuo. The crude product was dissolved in DCM and added dropwise with vigorous stirring to diethyl ether. The resulting precipitate was collected by filtration and washed with diethyl ether to give the PEG-bound intermediate polymer **4b** as yellow powder in quantitative yield (based on polymer recovery).

^{1}H NMR (300 MHz, $CDCl_3$): δ 8.41 (s, 2H), 7.69−7.75 (m, 4H), 7.52−7.57 (m, 4H), 7.12−7.23 (m, 4H), 6.84−6.94 (m, 4H), 4.13 (m, 4H, PEG-α-methylenes), 3.36−3.85 (bm, PEG); FT-IR (KBr): 1635, 1005 cm^{-1}.

PEG-bound intermediate polymer **4b** (244 mg, 0.05 mmol) was dissolved in 1.5 mL AcOH. NaOAc (12 mg, 0.15 mmol) and thiazolidine-2,4-dione (18 mg, 0.15 mmol) were added. The reaction vessel was sealed and heated to 120 °C for 12 h. After cooling to room temperature, the reaction mixture was poured into 8 mL water. The resulting precipitate was collected by filtration and washed with additional water and cold methanol to give product **5b** as a pale yellow powder.

^{1}H NMR (300 MHz, d_6-DMSO): δ 7.76 (s, 1H), 7.72 (d, J = 8.5 Hz, 2H), 7.53 (d, J = 8.5 Hz, 2H); ^{13}C NMR (100 MHz, d_6-DMSO): δ 167.48, 167.05, 132.29, 132.24, 131.76, 130.54, 124.35, 123.88; EI-MS: *m/z* 285/283 (1:1, M), 214/212 (1:1), 133; HRMS: calcd for $C_{10}H_6NSBrO_2$, 282.9302; found, 282.9296; HPLC purity (retention time): 100% (3.31 min); yield: 92% (pale yellow powder).

General Method for Preparation of Compounds 11{*1−4, 1−10*}. A smith process vial was charged with the PEG-bound intermediate polymer **4b** (4.88 g, 1 mmol), phenylboronic acid (293 mg, 2.4 mmol), K_2CO_3 (414 mg, 3 mmol), $Pd(OAc)_2$ (5 mg, 1 mol %), and 10 mL methanol. The reaction vessel was sealed and heated to 80 °C for 8 h. After cooling to room temperature, the reaction mixture was diluted and filtered. The filtrate was concentrated in vacuo. The crude product was dissolved in DCM and added dropwise with vigorous stirring to diethyl ether. The resulting precipitate was collected by filtration and washed with isopropanol and diethyl ether to give the PEG-bound intermediate polymer **6** as gray powder in 96% yield (based on polymer recovery).

^{1}H NMR (300 MHz, $CDCl_3$): δ 8.51 (s, 2H), 7.92−7.96 (m, 4H), 7.63−7.70 (m, 8H), 7.37−7.48 (m, 6H), 7.16−7.24 (m, 4H), 6.87−6.96 (m, 4H), 4.15 (m, 4H, PEG-α-methylenes), 3.39−3.86 (bm, PEG); IR (KBr): 1630 cm^{-1}.

Polymer-bound intermediate polymer **6** (244 mg, 0.05 mmol) was dissolved in 1.5 mL AcOH. NaOAc (12 mg, 0.15 mmol) and thiazolidine-2, 4-dione (18 mg, 0.15 mmol) were added. The reaction vessel was sealed and heated to 120 °C for 12 h. After cooling to room temperature, the reaction mixture was poured into 8 mL water. The resulting precipitate was collected by filtration and washed with additional water and cold methanol to give product **11**{*1, 1*} as a brown powder.

^{1}H NMR (300 MHz, d_6-DMSO): δ 7.83 (m, 3H), 7.72 (d, J = 8.5 Hz, 2H), 7.66 (m, 2H), 7.46−7.51 (m, 2H), 7.38−7.42 (m, 1H); ^{13}C NMR (100 MHz, d_6-DMSO): δ 167.91, 167.33, 141.95, 138.94, 132.16, 131.59, 130.89, 129.28, 128.42, 127.56, 126.95, 123.34; EI-MS: *m/z* 281 (M), 210, 165; HRMS: calcd for $C_{16}H_{11}NSO_2$, 281.0510; found, 281.0510; HPLC purity (retention time): 100% (3.66 min); yield: 86% (brown powder).

Library Assay against PTP1B. A colorimetric high-throughput assay for inhibitive activity against PTP1B was performed in 96-well plates. Briefly, the tested compounds were solubilized in DMSO at 250 μg/mL, and 2 μL samples were distributed to A2-H11 wells of 96-well clear polystyrene plate (Corning, Action, MA). The DMSO (2 μL) was distributed to A1-D1 and E12-H12 wells as the full enzyme activity, and orthovanadate (12.5 mM, 2 μL) was distributed to E1-H1 and A12-D12 wells as the positive inhibition. After adding an assay mixture (88 μL), 10 μL of the GST-PTP1B (300 nM) was added to initiate the reaction. The high-throughput screening was carried out in a final 100 μL volume containing 50 mM MOPS, pH 6.5, 2 mM pNPP, 30 nM PTP1B, and 2% DMSO, and the catalysis of pNPP was continuously monitored on a SpectraMax 340 microplate reader at 405 nm for 2 min at 30 °C. For calculating IC_{50}, inhibition assays were performed with 30 nM recombinant enzyme, 2 mM pNPP in 50 mM MOPS at pH 6.5, and the inhibitors diluted around the estimated IC_{50} values. IC_{50} was calculated from the nonlinear curve fitting of percent inhibition (inhibition (%)) vs inhibitor concentration [I] by using the following equation inhibition (%) = $100/\{1 + (IC_{50}/[I])k\}$, where k is the Hill coefficient.

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Supporting Information Available. Characterization data as yield, ^{1}H NMR, EI-MS, HPLC purities of all compounds in the library and ^{1}H NMR spectra of **11**{*1−4*, *1−10*}. Typical compounds were characterized by ^{13}C NMR and HRMS. This material is available free of charge via the Internet at http://pubs.acs.org.

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