Expedient Lewis Acid Catalyzed Synthesis of a 3-Substituted 5-Arylidene-1-methyl-2-thiohydantoin Library

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Received June 26, 2007

An efficient and rapid solution phase combinatorial synthesis of a 3-substituted 5-arylidene-1-methyl-2-thiohydantoin library was developed. The salient feature for this library production procedure is the addition of the Lewis acid catalyst, indium(III) trifluoromethanesulfonate, which serves to facilitate the direct condensation of aldehydes with 3-substituted 1-methyl-2-thiohydantoins. Use of this Lewis acid catalyst has resulted in faster reaction times, higher conversions and better purity profiles for these condensation reactions as compared to traditional uncatalyzed reactions. The resulting 315 member library of 3-substituted 5-arylidene-1-methyl-2-thiohydantoin is described.

Introduction

Indium(III) trifluoromethanesulfonate has recently come to light as a versitile reagent for organic synthesis.[1] Recent work by ourselves[2] and others[3] has established indium(III) salts as exceptionally useful Lewis acid catalysts for the Knovenengel type condensation of aldehydes, ketones, and alkynes[3b] with active methylene compounds such as hydantoins, thiohydantoins,[2a] oxindoles,[2a] and barbituic acid.[3a] The 3-substituted 5-arylidene-1-methyl-2-thiohydantoin moiety **3** (Scheme 1) is known to be a biologically active heterocyclic core in areas of antimycobacterial,[4] antiviral,[5] and anticonvulsant indications[6] and for the treatment of schistosomiasis infections[7] (Figure 1). As part of our efforts to generate chemical libraries of medicinally relevant compounds, we set out to prepare a focused library that elaborated on this interesting core. Recently Khodair and Nielsen[8] has reported the preparation of a small 28-member library of 3-substituted 5-arylidene-1-methyl-2-thiohydantoins **3** via microwave mediated conditions and traditional reflux conditions with good results. While the use of microwave heating conditions has proven invaluble for many reactions, there are a number of potential drawbacks for its use in parallel synthesis. These include the cost of the microwave instrumentation, as well as the fact that the majority of existing microwave reactors are designed to heat one reaction at a time. While this can be mediated somewhat by the use of robotics to load and unload reaction vessels, it is, nevertheless, a productivity bottleneck. We consider this impractical for the final diversification step for a library of several hundreds of compounds in a time efficient manner.

Our longstanding interest in parallel synthesis and library production prompted us to develop a methodology that was compatable with standard, low cost parallel synthesis equipment and techniques. Ideally, the chemistry would occur at room temperature or require only minimal heating and would be insensitive to atmospheric moisture and oxygen. Our initial approach for the preparation of this previously unreported library of 3-substituted 5-arylidene-1-methyl-2-thiohydantoins **5** involved the direct condensation of aldehydes with 3-substituted 1-methyl-2-thiohydantoins **3** in the presence of an organic base and a solvent such as toluene or 1,4-dioxane. Our observations showed that, in general, uncatalyzed reactions involving reactive aldehydes gave modest to good yields of 40–80% while less reactive aldehydes gave much lower yields; similar results are reported in the literature for other carbonyl containing substrates.[9–15] While this direct condensation procedure would have been sufficient to prepare a library with a limited diversity set of aldehydes, we needed to develop a reproducible synthetic procedure that allowed for the incorporation of these otherwise unreactive aldehydes. Next, we surveyed as series of Lewis acids, including $AlCl_3$, $BF_3 \cdot Et_2O$, $InCl_3$, $In(OTf)_3$, $Y(OTf)_3$, and $Sc(OTf)_3$, as potential catalysts for this reaction. Of these Lewis acids investigated, indium triflate consistently gave the highest yields and cleanest

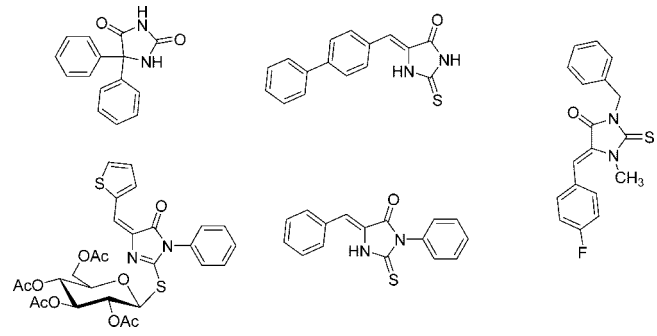

Figure 1. Structural analogues of compounds related to 3-substituted 5-arylidene-1-methyl-2-thiohydantoins investigated for potential biological activity.

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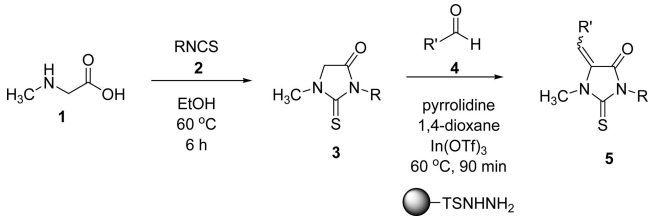
10.1021/cc700103u CCC: $37.00 © 2007 American Chemical Society
Published on Web 09/15/2007

Scheme 1. General Strategy for the Synthesis of 3-Substituted 5-Arylidene-1-methyl-2-thiohydantoins **5**



reaction products.[16] These observations are in agreement with Ranu et al. who observed that $InCl_3$ was a superior Lewis acid catalyst as opposed to $FeCl_3$, $TiCl_4$, $AlCl_3$, or $ZnCl_2$ for condensation reactions with carbonyl compounds.[17] The excellent reactivity of indium triflate, combined with its ease of handling, low toxicity, and stability to moisture make it a superior catalyst for the formation of arylidine thiohydantoins.

We herein describe our synthetic protocol for the preparation a 315 member library of 3-substituted 5-arylidene-1-methyl-2-thiohydantoins by the condensation of aldehydes with 3-substituted 1-methyl-2-thiohydantoins catalyzed by indium(III) trifluoromethanesulfonate.

Results and Discussion

Scheme 1 depicts the synthesis of 3-substituted 5-arylidene-1-methyl-2-thiohydantoins **5**. Using an Argonaut Quest synthesizer, the core compound intermediates **3**{*1–15*} were prepared in a parallel format by treating sarcosine **1** with a variety of isothiocyanates **2**{*1–15*} (Figure 3) in ethanol at reflux for several hours.[18] Upon cooling of the reaction mixture, the resulting solids were collected on the internal porous frit of the apparatus and washed with ethanol and diethyl ether to give the target core compounds **3**{*1–15*} in good yield. For compounds that were <95% purity, flash chromatography with silica gel afforded pure materials. Each of these intermediates were isolated and fully characterized by ^1H and ^{13}C NMR spectroscopy as well as high resolution mass spectrometry.

With the synthesis of the core intermediates complete, our next goal was to elucidate a parallel synthetic protocol suitable for the direct condensation of 3-substituted 1-methyl-2-thiohydantoins **3** with a diverse set of aldehydes **4**. Our initial approach optimized three critical reaction conditions: temperature, organic base, and solvent. The model reaction that we chose to investigate was the condensation reaction between thiohydantoin **3**{*11*} and aldehyde **4**{*17*} with the addition of pyrrolidine as the organic base. Test reactions were conducted in sealed 2-dram vials; J-Kem 24-well heater blocks were used to control the reaction temperature.

A full matrix of reaction conditions between temperature (25 °C and 60 °C) and solvent (acetonitrile, 1,2-dichlorobenzene, 1,2-dichloroethane, 1,1,2,2-tetrachloroethane, *N*-methylpyrrolidone (NMP), dimethylformamide, DMA (*N*,*N*-dimethylacetamide), tetrahydrofuran (THF), toluene, chloroform, and 1,4-dioxane) was assessed (monitored by UV-HPLC at 220 and 254 nm) to determine optimal conditions resulting in the highest degree of conversion and overall purity of the reaction mixture. After 12 h at 25 °C the condensation reaction showed little conversion to the desired products regardless of solvent. Increasing the reaction temperature from 25 °C to 60 °C resulted in reaction yields of 40–80% with reactive aldehydes; however, unreactive aldehydes typically gave very poor results. Results from varying the solvent indicated that both 1,4-dioxane and THF were found to be acceptable solvents under the test conditions. Other solvents such as acetonitrile, NMP, DMA, and toluene gave very low conversion to desired products even at 60 °C. Both THF and 1,4-dioxane were acceptable solvents for this reaction, with 1,4-dioxane as the preferred solvent due to the higher boiling point (99 °C). We found no appreciable difference on the extent of reaction between the use of pyrrolidine and piperidine as the organic base, and as such pyrrolidine was chosen as our standard base.

To determine the scope of aldehydes that could be incorporated into the library diversity set, using the standard conditions of 1,4-dioxane, pyrrolidine, and 60 °C, aldehydes **4**{*16–20*} underwent the direct condensation with 3-(4-methoxy-phenyl)-1-methyl-2-thiohydantoin **3**{*11*} to give compounds **5**{*11,16–20*}. As expected, reaction yields varied greatly depending on the reactivity and steric bulk of the corresponding aldehyde. While isovanillin **4**{*17*} gave **5**{*11,17*} with a yield of 62%, 1,4-benzodioxan-6-carboxaldehyde **4**{*18*} and thiophene-2-carboxaldehyde **4**{*19*} were somewhat less reactive, providing yields of 52 and 45% for **5**{*11,18*} and **5**{*11,19*}, respectively. *p*-Dimethylaminobenzaldehyde **4**{*16*} and 4-(1-pyrrolidinyl)benzaldehyde **4**{*20*} were particularly problematic, giving only 27% and 16% yields of **5**{*11,16*} and **5**{*11,20*}, respectively.

Because a library chemset of aldehydes that excluded unreactive reagents such as **4**{*4*}, **4**{*14*}, and **4**{*15–21*} would greatly limit the diversity of the final library, we set out to investigate the effect of a Lewis acid catalyst on the condensation reaction. After an intial survey of several Lewis acids ($AlCl_3$, $BF_3 \cdot Et_2O$, $InCl_3$, $In(OTf)_3$, $Y(OTf)_3$, and $Sc(OTf)_3$), indium(III) trifluoromethanesulfonate, boron trifluoride diethyletherate, and aluminum trichloride were all considered potential catalysts for this condensation reaction. As shown in Figure 2, indium(III) triflate, at a catalyst loading of 6–10 mol %, exhibited the greatest conversion among the Lewis acids surveyed for condensation reaction of aldehydes **4**{*16–20*} with **3**{*11*}. Most significant was the increase in overall yield to nearly 90% for all aldehydes studied. Particularly noteworthy was the increase to 89% and 93% conversion for aldehydes **4**{*16*} and **4**{*20*}, respectively. While it was not within the scope of this work to determine the *E* to *Z* isomer formation and ratio of the resulting 3-substituted 5-arylidene-1-methyl-2-thiohydantoins, in some cases both isomers were detected by HPLC/MS analysis and a subset was identified by ^1H NMR analysis that was in agreement with previously reported data for similar compounds.[12]

Library Synthesis

All parallel synthetic reactions were conducted in 24-well 2-dram glass vials fitted with teflon lined caps. Treatment of **3**{*1–15*} (570 μmol) in 1,4-dioxane (1.5 mL) with 1.2-fold excess of aldehydes **4**{*1–21*} (680 μmol) in the presence of pyrrolidine (1130 μmol) and indium(III) trifluoromethane-

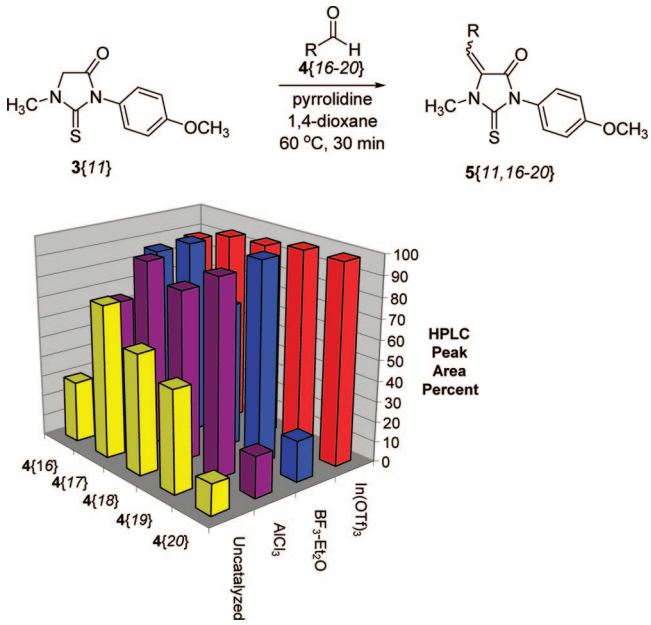


Figure 2. Extent of product formation for the condensation reaction of aldehydes **4**{*16–20*} with 3-(4-methoxy-phenyl)-1-methyl-2-thiohydantoin **3**{*11*} (peak area percent from analytical RP-HPLC/MS monitored via UV absorbance at 220 and 254 nm) with and without the addition of catalysts.

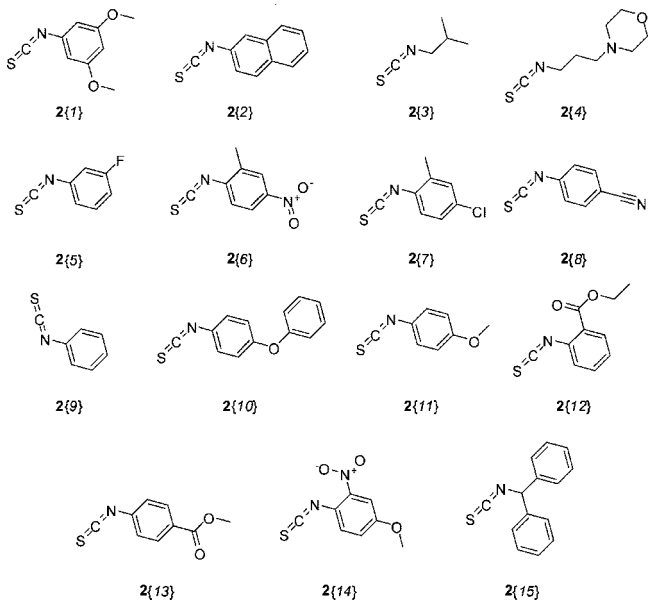


Figure 3. Reagent set of substituted isothiocyanates **2** used to incorporate diversity at the 3-position of the 3-substituted 5-arylidene-1-methyl-2-thiohydantoins **5**.

sulfonate (35 μmol, 6 mol %) provided the desired 3-substituted 5-arylidene-1-methyl-2-thiohydantoins **5**. The selection of polar and nonpolar aldehydes **4**{*1–21*} included a variety of aliphatic, carbocyclic, heterocyclic, and substituted benzaldehydes (Figure 4) which were chosen to give an optimal distribution of molecular weight and cLogP of the final compounds as shown in Figure 5.

The condensation reaction was usually complete after 30 min at 60 °C; however, to ensure reaction completion, reactions were heated for a total of 1.5 h. In most cases LC/MS and TLC analysis of the crude reaction mixtures indicated that all starting 3-substituted 1-methyl-2-thiohydantoins **3** were converted to **5**

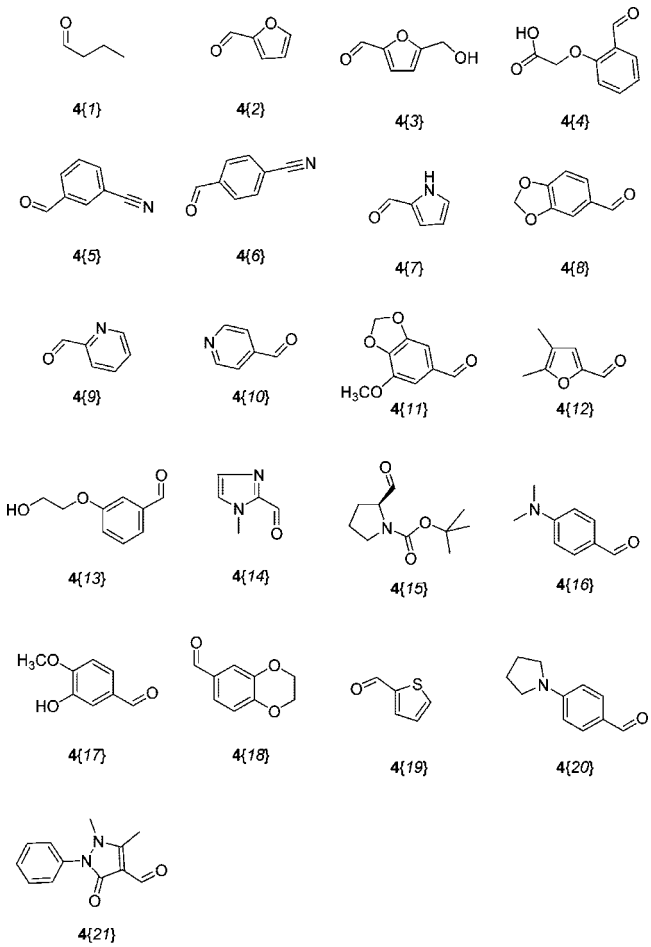


Figure 4. Reagent set of aldehydes **4** used to incorporate diversity at the 5-position of the 3-substituted 5-arylidene-1-methyl-2-thiohydantoins **5**.

and the only other components of the reaction mixture were excess aldehyde **4** and pyrrolidine. Workup and the purification protocol (Scheme 1) included scavenging of the excess aldehyde using polymer bound *p*-toluenesulfonyl hydrazide resin (PS-TSNHNH$_2$) and agitating the crude reaction mixture for 6 h at room temperature. The reaction mixtures were then diluted with ethyl acetate, filtered to remove the resin, and washed with saturated sodium bicarbonate. Final purification was achieved by passing the resultant reaction mixture through a pad of silica gel. This rapid purification synthetic strategy resulted in the preparation of a diverse library of 3-substituted 5-arylidene-1-methyl-2-thiohydantoins **5**; 268 compounds (85.1%) were above 80% purity with an average HPLC purity (UV at 220 nm) of 93% and a 35 mg weight. The purity and identity of compounds were confirmed by LC/MS analysis of all of the library products as well as representative ^{1}H NMR analysis of 10% of the products. The library of 3-substituted 5-arylidene-1-methyl-2-thiohydantoins **5** is likely to have physicochemical properties suitable for biological study based on the cLogP distribution (2–5) and molecular weight distribution (325–500 amu) as depicted in Figure 5.

Conclusion

Numerous literature references cite the potential for the 3-substituted 5-arylidene-1-methyl-2-thiohydantoins to be chemical entities suitable for drug discovery. In summary, we have developed a robust solution phase synthetic method

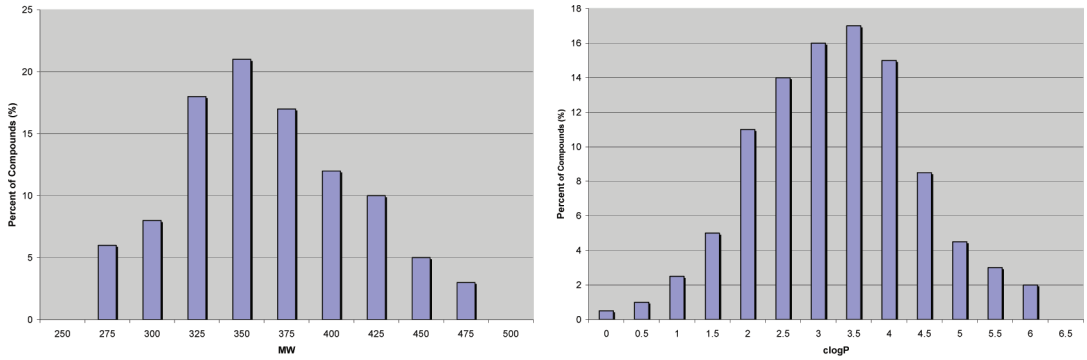


Figure 5. cLogP and molecular weight distribution analysis of the 315 compounds comprising the 3-substituted 5-arylidene-1-methyl-2-thiohydantoins **5** library.

for the preparation of this interesting class of compounds. Key to the synthetic strategy to overcome the unreactive nature of some aldehydes necessary for the diversification of the library was addition of the Lewis acid catalyst, indium(III) trifluoromethanesulfonate. Indium(III) triflate was chosen as the catalyst for the library synthesis as a result of the scope of application, ease of handling, air stability, reproducible results, low toxicity, and cost. Subsequent scavenging of the excess aldehyde with a solid phase resin and aqueous basic extraction afforded target compounds in high purity and yields.

Experimental Section

General Information. All reagents were obtained from commercial sources and used without further purification. All solvents were HPLC grade and obtained from Fisher Scientific. Isothiocyanates **2**{*1–15*} and aldehydes **4**{*1–21*} were purchased from Sigma-Aldrich Co., Lancaster, Acros Organics, or Maybridge Scientific. PS-TSNHNH$_2$ resin (3.65 mmol/g loading) was purchased from Argonaut. Silica gel 60 (particle size 40–63 μm) was purchased from Krackler.

The LC/MS data were recorded on a Perkin-Elmer Sciex APCI single quadropole mass spectrometer with Shimadzu LC-8a HPLC pumps. Chromatograms were recorded with UV detection at 220 and 254 nm using a Phenomenex Luna, 5 μm C8 column (100 × 4.60 mm). Two mobile phases (A, 99.98% water, 0.02% TFA; B, 99.98% acetonitrile, 0.02% TFA) were used as a gradient for 30% B to 95% B in 4.0 min and 30% B for 2.0 min with a flow rate of 2.0 mL/min. ^{1}H NMR spectra were recorded in 5 mm tubes on a 300 MHz Bruker Avance in DMSO-d_6 or $CDCl_3$. Chemical shifts are reported in δ units (ppm) downfield from TMS as an internal standard.

Synthesis of the library was performed in 2-dram glass vials fitted with Teflon lined caps. The products were transferred into tared bar-coded vials using an Apogent Matrix 6-channel pipet (Portsmouth, NH) and weighed using the Mettler-Toledo Bohdan USP (Mount Vernon, IL). Solvents were removed using a Genevac HT-12 with heating at 45 °C and a 0.5 torr vacuum using a VacRamp-4 program over 4 h.

3-Substituted 1-Methyl-2-thiohydantoins 3{1–15}. General Procedure.[14] To an Argonaut Quest synthesizer fitted with a magnetic stir bar was charged sarcosine (**1**, 2.0 g, 22.4 mmol) and anhydrous ethanol (20 mL). To the resulting solution was added the appropriate isothiocyanate (1.0 equiv, 22.4 mmol), and the reaction mixture was heated at 60 °C for 2 h after which time the mixture was allowed to cool to room temperature and the resulting solids were collected on the internal frit of the apparatus. The solid residue was washed with ethanol (10 mL) and diethyl ether (25 mL). If the resulting crude product was <95% purity, it was dissolved into a minimum of CH_2Cl_2 (15 mL) and purified by silica gel chromatography (50 g) with ethyl acetate/hexanes (1:4) to give the title compound.

Arylidene Thiohydantoins Catalyst Survey. To a 2 dram vial fitted with a magnetic stir bar was added the appropriate thiohydantoin (**3**, 0.75 mmol), aldehyde (**4**, 1.2 equiv, 0.90 mmol), pyrrolidine (1.5 equiv, 1.13 mmol) ,and 1,4-dioxane (1.5 mL). To the reaction mixture was added the desired catalyst (0.1 equiv, 0.075 mmol), and the reaction mixture was heated to 60 °C using a 24-well J-Kem heater block. The reactions were concentrated to dryness under reduced pressure, and the crude residue was purified by silica gel (10 g) chromatography with an eluent system of CH_2Cl_2/CH_3OH (95:5) to give the title compound.

Library Synthesis. A solution of each 3-substituted 1-methyl-2-thiohydantoin in 1,4-dioxane (0.380 M, 1.5 mL, 0.570 mmol) was dispensed into 2-dram glass vials. Aldehydes (0.680 mmol, 1.2 equiv), pyrrolidine (0.095 mL, 1.13 mmol, 2 equiv), and indium(III) trifluoromethanesulfonate (20 mg, 0.035 mmol, 6 mol %) were then added, the vials capped, and the reaction mixtures stirred at 60 °C for 1.5 h and then cooled to room temperature. Polymer bound *p*-toluenesulfonyl hydrazide resin (50 mg, 0.182 mmol) was added using a Radleys Titan 24 well resin loader, the mixture was shaken for 6 h, and the resin was removed by filtration through empty Silicycle 12 mL cartridges fitted with a polypropylene frit. The filtrate was collected in 4-dram glass vials, and the resin was rinsed with ethyl acetate (1 mL). Saturated aqueous sodium bicarbonate (2 mL) was added to the combined organics, and the mixture agitated for 10 min. The organic layer was removed and passed through a plug of silica gel (2 g), eluting with ethyl acetate (3 mL) and collecting the eluent in test tubes (16 × 100 mm). The products were transferred into tared bar-coded vials using an Apogent Matrix 6-channel pipet, and solvent was removed under vacuum using a ThermoSavant Discovey SpeedVac

evaporator. Finally the samples were weighed using the Mettler-Toledo Bohdan USP.

Acknowledgment. The authors thank Drs. Michael P. Trova and Douglas P. Kitchen for their helpful discussions and suggestions.

Supporting Information Available. ^{1}H and ^{13}C NMR data for novel compounds **3**{*1–15*} and representative ^{1}H NMR and LCMS spectra for chemset **5**{*1–15,1–21*} are presented. This material is available free of charge via the Internet at http://pubs.acs.org.

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CC700103U