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Efficient Synthesis of Novel γ-Substituted γ-Butenolides by Lewis Acid Catalyzed Addition of Metal Enolates of Active Methylene Compounds to Mucohalic Acids

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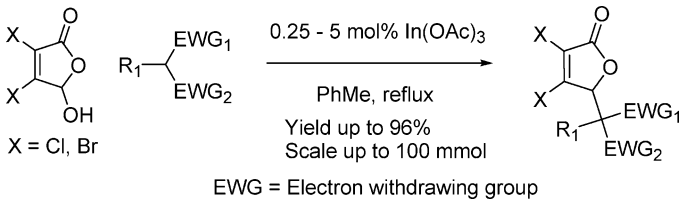
Received March 16, 2005



Lewis acid catalyzed addition of active methylene compounds to mucochloric acid (**1**) and mucobromic acid (**2**) affording Knoevenagel aldol adducts, γ-substituted γ-butenolides, has been explored. Catalytic efficiencies of various Lewis acids have been compared. Indium acetate (0.25−5 mol %) was found to be the most efficient catalyst.

Introduction

There has been a continuous interest in developing efficient and convenient methods for the synthesis of γ-butenolides[1] because these subunits are found in many natural products, as well as in a number of synthetic drug candidates with diverse biological activities (Figure 1).[2] Mucohalic acids (**1** and **2**, Figure 2) are two inexpensive, commercially available, and highly functionalized starting materials. The unique disposition of various functionalities makes them interesting building blocks for molecules of interest. However, they have remained underutilized in organic synthesis presumably as a result of the difficulty in the selective manipulation of the functional groups and their poor stability under basic conditions. In an effort to establish the relative reactivity

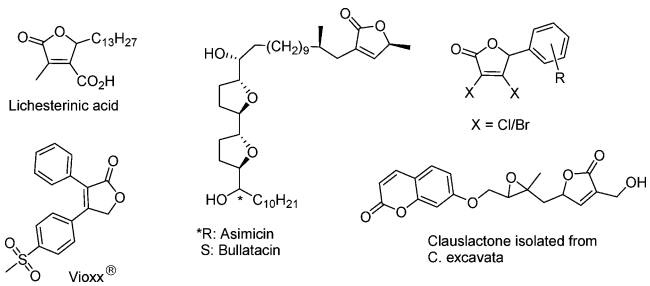


FIGURE 1. Natural and synthetic compounds with the γ-butenolide subunit.

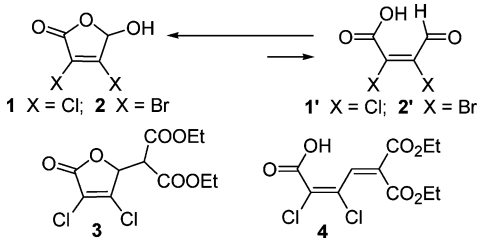


FIGURE 2. Mucochloric and mucobromic acids and related compounds.

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(1) (a) Sohn, S. S.; Rosen, E. L.; Bode, J. W. *J. Am. Chem. Soc.* **2004**, *126*, 14370. (b) Boye, A. C.; Meyer, D.; Ingison, C. K.; French, A. N.; Wirth, T. *Org. Lett.* **2003**, *5*, 2157. (c) Dangel, B. D.; Johnson, J. A.; Sames, D. *J. Am. Chem. Soc.* **2001**, *123*, 8149. (d) Morizawa, Y.; Hiyama, T.; Nazoki, H. *Tetrahedron Lett.* **1981**, *22*, 2297. (e) Evans, P. A.; Kennedy, L. J. *Org. Lett.* **2000**, *2,* 2213. (f) Takimoto, M.; Kawamura, M.; Mori, M. *Org. Lett.* **2003**, *5*, 2599. (g) Pearson, A. J.; Mesaros, E. F. *Org. Lett.* **2002**, *4*, 2001.

(2) (a) Meresse, P.; Dechaux, E.; Monneret, C.; Bertounesque, E. *Curr. Med. Chem.* **2004**, *11*, 2443.(b) Vogel, K.; Sterling, J.; Herzig, Y.; Nudelman, A. *Tetrahedron* **1996**, *52*, 3049. (c) Böhm, C.; Reiser, O. *Org. Lett.* **2001**, *3*, 1315. (d) Pohmakotr, M.; Harnying, W.; Tuchinda, P.; Reutrakul, V. *Helv. Chim. Acta* **2002**, *85*, 3792. (e) Avedissian, H. A.; Sinha, S. C.; Yazbak, A.; Sinha, A.; Neogi, P.; Sinha S. C.; Keinan, E. *J. Org. Chem.* **2000**, *65*, 6035. (f) Sinha, S. C.; Sinha, S. C.; Keinan, E. *J. Org. Chem.* **1999**, *64*, 7067. (g) Ito, C.; Itoigawa, M.; Katsuno, S.; Omura, M.; Tokuda, H.; Nishino, H.; Furukawa, H. *J. Nat. Prod.* **2000**, *63*, 1218. (h) Lattmann, E.; Ayuko, W. O.; Kinchinaton, D.; Langley, C. A.; Singh, H.; Karimi, L.; Tisdale, M. J. *J. Pharm. Pharmacol.* **2003**, *55*, 1259.

10.1021/jo050538t CCC: $30.25 © 2005 American Chemical Society
Published on Web 06/21/2005

among the functional groups, we have recently reported regioselective amination, etherification, reductive amination, arylation, allylation, and C−C bond formation by Mukaiyama aldol reaction of mucohalic acids.[3] To further explore mucohalic acid chemistry, this paper reports Lewis acid catalyzed Knoevenagel aldol addition of active methylene compounds to mucohalic acids to afford γ-functionalized γ-butenolides.

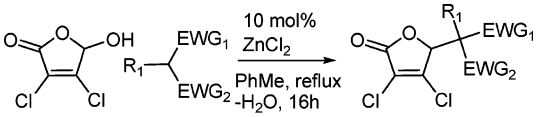
The Knoevenagel condensation is one of the most useful and classical methods for C−C bond formation in organic synthesis.[4] Usually a catalytic amount of ammonia or amine base is employed to promote the condensation of aldehyde or ketone with active methylene compounds. The use of Lewis acid to catalyze this reaction has begun to receive some attention in recent years but is still in its infancy.[5] All of these reports utilized simple aromatic aldehydes or ketones as the carbonyl component and the active methylene compounds lacked diversity. Also, there are few reported efforts to reduce the Lewis acid loading in this type of reaction. The instability of mucohalic acids under basic conditions prompted us to focus on Lewis acid catalyzed C−C bond forming reactions at the C-4 positions of mucohalic acids.[6]

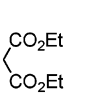
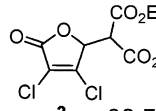
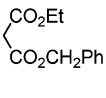
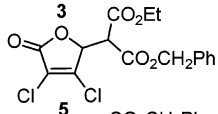
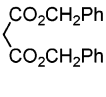
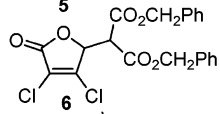
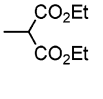
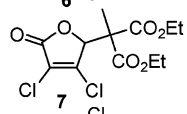
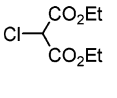
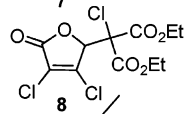
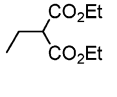
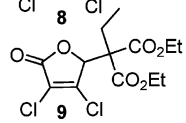
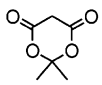
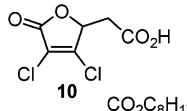
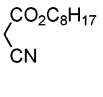
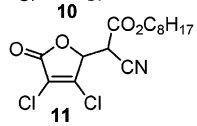
Results and Discussion

We initiated our study with **1** using diethyl malonate as the active methylene compound and $ZnCl_2$ as the Lewis acid.[7] Refluxing a mixture of **1** and $ZnCl_2$ (10 mol %) in toluene with water removal in a Dean−Stark condenser over 16 h resulted in 82% isolated yield of **3**. It is interesting to note that because of the unique disposition of the carboxylic acid group the aldol adduct cyclized (dehydration) and the isolated product is **3** not **4** (Figure 2). Similar observations were made during the reductive amination of mucohalic acids where α,β-unsaturated γ-butyrolactam was isolated.[3]

Without doubt, connecting mucohalic acid, a versatile building block, to a very useful and inexpensive three-carbon building block, diethyl malonate, is more meaningful.[8] The initial exciting result prompted us to explore different active methylene compounds that resulted in the isolation of Knoevenagel-type aldol addition products

TABLE 1. $ZnCl_2$-Catalyzed Knoevenagel Aldol Condensation with Mucochloric Acid[a]



Entry	$R_1CH(EWG_1)(EWG_2)$	Product	Yield[b]
1		 **3**	82
2		 **5**	81
3		 **6**	70
4		 **7**	92
5		 **8**	61[c]
6		 **9**	62
7		 **10**	71[d]
8		 **11**	86

[a] Reaction conditions: 10 mmol each of **1** and $R_1CH_2R_2$, 0.1 equiv of $ZnCl_2$, 50 mL of PhMe, refluxed for 16 h with water separation by Dean−Stark. [b] Products were isolated and purified by silica gel chromatography and characterized [c] The reaction was done for 24 h [d] Product crystallized out from the reaction mixture upon cooling

in good to excellent isolated yields (Table 1). Interestingly, the use of Meldrum's acid afforded the Doebner product via acetonide cleavage and decarboxylation (entry 7).[9] Though the yields were satisfactory, in some cases it was difficult to isolate the products from unconverted starting material (entries 2, 3, 5, 7 and 8) because of the close polarity of **1** and the corresponding products. Also, the reaction condition was not suitable for **2** as significant decomposition occurred at times. Our effort to reduce the amount of $ZnCl_2$ from 10 mol % was not successful because of longer reaction time and incomplete conversion.

For the future development of a chiral Lewis acid catalyst for chiral butenolide formation, it would be necessary to reduce the catalyst amount.[10] Therefore, we decided to investigate the effect of various Lewis acids on these transformations. It is known that a Lewis acid

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(6) Base-catalyzed condensations between mucohalic acids and active methylene compounds have been reported previously with poor yield (2−45%). See: Mowry, D. T. *J. Am. Chem. Soc.* **1953**, *75*, 1909 and correction at *J. Am. Chem. Soc.* **1954**, *76*, 6417.

(7) Initial results were presented in part at the 225th ACS National Meeting, New Orleans, LA, March 23−27, 2003.

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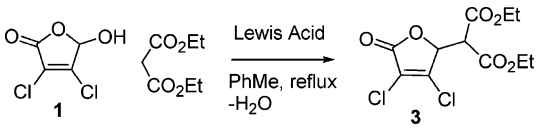
(9) Doebner, O. *Ber.* **1900**, *33*, 2140.

(10) *Lewis Acids in Organic Synthesis*; Yamamoto, H., Ed.; Wiley-VCH: New York, 2000.

TABLE 2. Effect of Lewis Acids on Knoevenagel Aldol Condensation with Mucochloric Acid[a]



entry	Lewis acid	mol %	% of **3** at 8 h[b]
1	$ZnCl_2$	10	80
2	$Zn(OTf)_2$	5	19
3	$BiCl_3$	10	32
4	$Mg(OTf)_2$	5	7
5	$Sc(OTf)_3$	5	60
6	$Yb(OTf)_3$	5	72
7	$AlCl_3$	10	68
8	$CoCl_2$	5	0
9	$ZrCl_4$	5	90
10	$In(ClO_4)_3 \cdot H_2O$	5	45
11	$In(OTf)_3$	5	52
12	$InBr_3$	5	71
13	InF_3	5	63
14	$InCl_3$	10	100 (3 h)
15	$InCl_3$	5	99 (6 h)
16	$InCl_3$	1	99
17	$In(OAc)_3$	5	100 (5.5 h)
18	$In(OAc)_3$	1	100 (95)[c]

[a] Reaction conditions: 10 mmol each of **1** and $CH_2(CO_2Et)_2$, LA, 50 mL of PhMe refluxed with water separation by Dean−Stark. [b] Measured by HPLC. [c] Isolated yield.

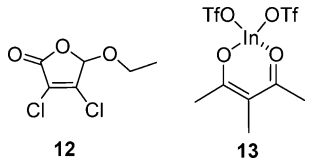


FIGURE 3. Side product and suggested In-enolate.

greatly shifts the tautomeric equilibrium between enol and keto forms and often favors the enol form by chelation. The enolate of an active methylene compound is responsible for its reactivity as a nucleophile. Thus, the reaction between **1** and diethyl malonate was performed using different Lewis acids (Table 2). Surprisingly, the best result was obtained with $InCl_3$ and $In(OAc)_3$. Yields were lower with other In(III) salts, such as $InBr_3$, InF_3, and $In(ClO_4)_3$. A substantial amount (10−20%) of the ethyl ether **12** formed when $In(OTf)_3$, $Sc(OTf)_3$, or $In(ClO_4)_3 \cdot H_2O$ was used as Lewis acid, presumably by hydrolysis of diethyl malonate and subsequent etherification of **1**. Though $ZrCl_4$ resulted in a good conversion, it is not very suitable from a practical standpoint because of its hygroscopic and corrosive nature.

The indium(III) salt, considered to be a novel, water-tolerant, and green Lewis acid, has received significant attention in recent years.[11] The most-utilized In(III) Lewis acids are indium chloride and indium triflate. Recently Nakamura and co-workers reported indium triflate catalyzed addition of active methylene compounds to 1-alkynes, where it was suggested that the formation of indium enolate (**13**, Figure 3) is essential for the catalytic cycle.[12] In this study, we found both indium chloride and indium acetate, especially $In(OAc)_3$, are superior to $In(OTf)_3$. Unlike indium chloride, $In(OAc)_3$ seldom received attention in organic synthesis until recently. For example, Li reported that using $In(OAc)_3$ to promote Grignard-type reactions,[13] aldol reactions, and Mannich-type reactions in water and protic solvents.[14] Recently Hosomi reported $In(OAc)_3$-catalyzed 1,4-reduction with $PhSiH_3$ in ethanol at ambient temperature.[15] In our study, we found that the loading of indium acetate can be as low as 1% and still give excellent yield of butenolide **4** (entry 19, HPLC conversion 100%, isolated yield 95%).

We have optimized the reaction on a larger scale (16.8 g of **1**, 100 mmol) and found this procedure is reliable and robust. Under air, a mixture of **1** (16.8 g, 100 mmol), diethyl malonate (16 g, 100 mmol), and $In(OAc)_3$ (0.25 mol %, 0.07 g) in reagent grade toluene (50 mL) was heated to reflux for 14 h, and water was removed via a Dean−Stark trap to afford butenolide **3** in 92% isolated yield.[16] Regarding the relatively nontoxic nature of the catalyst, its ease of handling, and the easy availability and low cost of both starting materials, it is difficult to envision a more ideal process in terms of green chemistry principles, experimental ease, practicality, and efficiency.

These $In(OAc)_3$ conditions were found to be general and efficient for the use of a variety of other active methylene compounds such as alkyl cyanoacetate, ethyl malonate monoamide, and ethyl nitroacetate (Table 3). With 5% $In(OAc)_3$ as catalyst, the reactions typically completed within 8 h and in some cases even faster (entry 11, 2.5 h). As a result of shorter reaction times, it became practical for more hindered substrates (entry 7). The yield was 10% lower with diethyl chloromalonate and $ZnCl_2$ (entry 5, Table 1) compared to that with $In(OAc)_3$ (entry 6, Table 3). It is also important to note that $ZnCl_2$ failed to yield any product with ethyl malonate monoamide and ethyl nitroacetate. Interestingly, neither $In(OAc)_3$ nor $ZnCl_2$ gave any product with acetyl acetone or ethyl acetoacetate under these reaction conditions.

Reactions between mucobromic acid **2** and active methylene compounds were found as effective as with **1** (Table 3). Simple malonates work well and gave the desired product with excellent isolated yield (entry 1). For a monosubstituted malonate such as diethyl methyl malonate (entry 5), the reaction time was longer (12 h) and the yield was lower (78%) using **2** compared to that with **1**, presumably as a result of steric hindrance caused by a larger Br atom at the β-position. Nevertheless, $In(OAc)_3$ proved to be milder than $ZnCl_2$ in promoting this transformation.

On the basis of the experimental results and known literature examples, a possible reaction pathway is given (Figure 4). An indium enolate generated from indium acetate and an active methylene compound is critical for the catalytic cycle. The released acetic acid is useful to enrich activated species **24**. The role $In(OAc)_3$ plays is perhaps 3-fold: (a) generating indium enolate, (b) generating acetic acid, and (c) catalyzing the dehydration to

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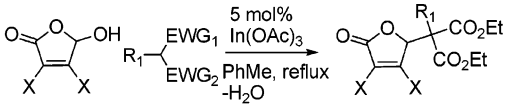
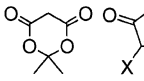
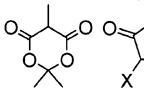
(16) With 0.5 mol % $In(OAc)_3$, the reaction was over in 7 h and the isolated yield was 96%.

TABLE 3. In(OAc)$_3$ Catalyzed Knoevenagel Aldol Condensation with Mucohalic Acids[a]



Entry	$R_1CH(EWG_1)(EWG_2)$	Product	Time (h)	Yield[b]
1	$CH(CO_2Et)_2$	**3**, X = Cl	8	95
		14, X = Br	4	89
2	$CH(CO_2{}^iPr)_2$	**15**, X = Cl	8	92
		16, X = Br	5	91
3	$CH(CO_2Et)(CO_2CH_2Ph)$	**5**, X = Cl	8	95
		17, X = Br	4	89
4	$CH(CO_2CH_2Ph)_2$	**6**, X = Cl	8	85
5	$CH_3CH(CO_2Et)_2$	**7**, X = Cl	7	92
		18, X = Br	12	78
6	$ClCH(CO_2Et)_2$	**8**, X = Cl	23	71
7	$CH_3CH_2CH(CO_2Et)_2$	**9**, X = Cl	24	65
8		**10**, X = Cl	8	80[c]
		19, X = Br	7	60[c]
9		**20**, X = Cl	6	90
10	$CH(CO_2C_8H_{17})(CN)$	**11**, X = Cl	26	90
		21, X = Br	23	69
11	$CH(CO_2Et)(CONH_2)$	**22**, X = Cl	2.5	75
12	$CH(CO_2Et)(NO_2)$	**23**, X = Cl	24	70

[a] Reaction conditions: 10 mmol each of **1**/**2** and $R_1CH_2R_2$, 0.05 equiv of In(OAc)$_3$, and 50 mL of PhMe, reluxed with water separation by Dean−Stark. [b] Products were isolated and purified by silica gel chromatography and characterized. [c] Product crystallized out from the reaction mixture upon cooling.

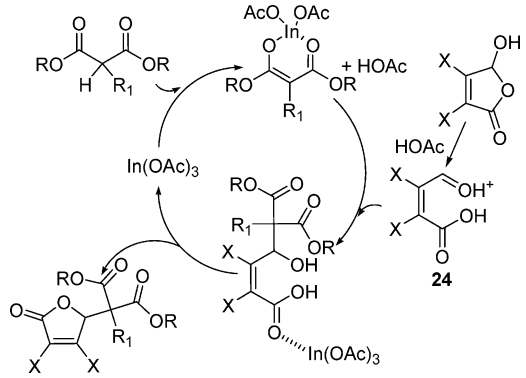


FIGURE 4. Proposed catalytic cycle.

form the butenolide **3**. It is easy to understand why indium triflate is not as good as indium acetate because the free CF_3SO_3H is a strong acid that can catalyze (with help from indium triflate) the hydrolysis of diethyl malonate, thus forming the side product **12**. Because the Knoevenagel condensation product, **4**, was not formed (when diethyl methyl malonate was used, it is impossible to form **4** or the diene-acid[17]), we consider this reaction a Knoevenagel aldol reaction as the reaction product remains at the aldol product stage.[18]

Conclusions

In summary, we have developed a simple, efficient, and highly practical method to promote the Knoevenagel aldol reaction where mucohalic acids are used as starting material, giving γ-functionalized γ-butenolides in good to excellent yield. Indium acetate turned out to be a novel, green Lewis acid to promote this reaction for addition of diverse types of active methylene compounds such as dialkyl malonate, alkyl cyanoacetate, ethyl malonate monoamide, and ethyl nitroacetate to mucochloric acid. To the best of our knowledge, this is the first report of a Knoevenagel aldol condensation reaction catalyzed by In(OAc)$_3$. We have been able to minimize the consumption

(17) It is unlikely to form diene-acids such as **4** even when R_1 = H because these types of compounds are very unstable with heat and expected to undergo decarboxylation that would produce other side products. See: Al-Hakim, A.; Haines, A. H. *Tetrahedron Lett.* **1982**, *23*, 5295.

(18) Marumoto, S.; Kogen, H.; Naruto, S. *Chem. Commun.* **1998**, 2253.

of $In(OAc)_3$ to 0.25 mol % and establish the efficiency of this methodology by performing the reaction at larger scale. Further investigations, including extension of the use of these building blocks and indium enolates in organic synthesis and exploring the generality of this methodology with diverse carbonyl compounds, will be reported in due course.

Experimental Section

All reactions were carried out under nitrogen atmosphere unless otherwise noted.

General Procedure for Compounds 3, 4−9, 11−18, and 21−23. A mixture of mucohalic acid (10 mmol), $In(OAc)_3$ (0.5 mmol), and the active methylene compound (10 mmol) in 50 mL of toluene was refluxed with water separation in a Dean−Stark condenser. The reaction mixture was concentrated under reduced pressure. The residue was purified by silica gel column chromatography using ethyl acetate/hexanes as eluent.

General Procedure for Compounds 10 and 19. A mixture of mucohalic acid (10 mmol), $In(OAc)_3$ (0.5 mmol), and the active methylene compound (10 mmol) in 50 mL of toluene was refluxed. No water separation was observed in the Dean−Stark condenser. The reaction mixture was filtered hot and concentrated to half. The product crystallized out upon cooling.

Procedure for Compound 20. Similar to the procedure for **10** and **19** except that the product did not crystallize out. The reaction mixture was cooled to room temperature, and 50 mL of ^{t}butyl methyl ether was added to it. The organic phase was sequentially washed with 2 N HCl (2 × 10 mL) and brine (10 mL), dried over anhydrous Na_2SO_4, and filtered, and the filtrate was concentrated under high vacuum to yield the desired product of sufficiently high purity.

Diethyl 2-(3,4-Dichloro-5-oxo-2,5-dihydro-furan-2-yl)-malonate (3). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 5.56 (d, J = 4.49 Hz, 1H), 4.23 (m, 4H), 3.93 (d, J = 4.49 Hz, 1H), 1.25 (m, 6H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 165.0, 164.2, 149.7, 122.9, 79.0, 62.9, 52.9, 14.1. Anal. Calcd for $C_{11}H_{12}Cl_2O_6$: C, 42.47; H, 3.89. Found: C, 42.39; H, 3.79.

Benzyl Ethyl 2-(3,4-Dichloro-5-oxo-2,5-dihydro-furan-2-yl)-malonate (5, diastereomeric mixture). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.35 (m, 5H), 5.58 and 5.57 (d, J = 3.51 Hz, 1H), 5.20 (m, 2H), 4.23 (m, 2H), 3.99 and 3.94 (d, J = 4.48 Hz, total 1H), 1.22 (m, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 165.4, 165.0, 164.1, 144.6, 134.6, 129.1, 128.9, 128.7, 123.0, 78.9, 68.5, 63.0, 62.9, 52.9, 52.8, 14.1. Anal. Calcd for $C_{16}H_{14}Cl_2O_6$: C, 51.50; H, 3.78; Cl, 19.00. Found: C, 51.68; H, 3.65; Cl, 19.20.

Dibenzyl 2-(3,4-Dichloro-5-oxo-2,5-dihydro-furan-2-yl)-malonate (6). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.33 (m, 6H), 7.27 (m, 4H), 5.56 (d, J = 4.48 Hz, 1H), 5.20 (d, J = 1.75 Hz, 2H), 5.15 (s, 2H), 4.03 (d, J = 4.48 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 164.7, 164.6, 149.4, 134.5, 128.9, 128.8, 128.7, 123.0, 78.9, 68.6, 52.8. Anal. Calcd for $C_{21}H_{16}Cl_2O_6$: C, 57.95; H, 3.71; Cl, 16.29. Found: C, 57.61; H, 3.51; Cl, 16.54.

Diethyl 2-(3,4-Dichloro-5-oxo-2,5-dihydro-furan-2-yl)-2-methyl-malonate (7). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 5.74 (s, 1H), 4.23 (m, 4H), 1.43 (s, 3H), 1.26 (m, 6H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 167.2, 164.4, 150.1, 123.4, 83.0, 63.0, 62.8, 56.7, 15.4, 14.1. Anal. Calcd for $C_{12}H_{14}Cl_2O_6$: C, 44.33; H, 4.34. Found: C, 44.45; H, 4.18.

Diethyl 2-Chloro-2-(3,4-dichloro-5-oxo-2,5-dihydro-furan-2-yl)-malonate (8). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 6.02 (s, 1H), 4.37 (m, 4H), 1.34 (m, 6H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 163.7, 162.6, 147.8, 125.1, 82.4, 70.8, 64.7, 14.1. Anal. Calcd for $C_{11}H_{11}Cl_3O_6$: C, 38.23; H, 3.21; Cl, 30.78. Found: C, 38.53; H, 2.96; Cl, 30.94.

Diethyl 2-(3,4-Dichloro-5-oxo-2,5-dihydro-furan-2-yl)-2-ethyl-malonate (9). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 5.52 (s, 1H), 4.25 (m, 2H) 4.16 (m, 2H), 2.17 (m, 2H) 1.26 (t, J = 7.24 Hz, 3H), 1.20 (t, J = 7.23, 3H) 1.02 (t, J = 7.52, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 169.7, 167.6, 166.8, 151.5, 122.6, 82.5, 62.5, 61.2, 53.8, 26.8, 14.2, 9.4. Anal. Calcd for $C_{13}H_{16}Cl_2O_6$: C, 46.04; H, 4.75; Cl, 20.91. Found: C, 46.00; H, 4.66; Cl, 21.07.

(3,4-Dichloro-5-oxo-2,5-dihydro-furan-2-yl)-acetic Acid (10). ^{1}H NMR (400 MHz, DMSO-d_6) δ: 12.89 (br. S, 1H), 7.11 (s, 1H), 3.62 (s, 2H). ^{13}C NMR (100 MHz, DMSO-d_6) δ: 167.6, 165.9, 147.9, 124.0, 92.7, 41.7. IR (KBr): 3001, 2910, 1794, 1702, 1637 cm^{-1}. Anal. Calcd for $C_6H_4Cl_2O_4$: C, 34.15; H, 1.91. Found: C, 33.51; H, 1.70.

Octyl Cyano-(3,4-dichloro-5-oxo-2,5-dihydro-furan-2-yl)-acetate (11, diastereomeric mixture). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 5.56 (d, J = 2.53 Hz, 70% of 1H), 5.53 (d, J = 3.51 Hz, 30% of 1H), 4.30 (t, J = 6.92 Hz, 1H), 4.26 (m, 1H), 4.16 (m, 1H), 1.69 (m, 2H), 1.30 (m, 10H), 0.86 (br t, J = 8.0 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 163.1, 161.9, 161.3, 147.4, 124.6, 110.5, 78.3, 68.9, 40.7, 31.91, 29.3, 28.4, 25.8, 22.8, 14.3. Anal. Calcd for $C_{15}H_{19}Cl_2NO_4$: C, 51.74; H, 5.50; N, 4.02; Cl, 20.36. Found: C, 51.61; H, 5.39; N, 4.03; Cl, 20.25.

3,4-Dichloro-5-ethoxy-5*H*-furan-2-one (12).[19] ^{1}H NMR (400 MHz, $CDCl_3$) δ: 5.79 (s, 1H), 3.89 (m, 1H), 3.79 (m, 1H), 1.30 (t, J = 7.13 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 163.4, 147.7, 124.5, 101.0, 66.3, 15.1. LRMS (GC) m/z: 196 (M^+)

Diethyl 2-(3,4-Dibromo-5-oxo-2,5-dihydro-furan-2-yl)-malonate (14). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 5.55 (d, J = 4.30 Hz, 1H), 4.26 (m, 2H), 4.21 (m, 2H), 3.96 (d, J = 4.30 Hz, 1H), 1.29 (t, J = 7.23, 3H), 1.23 (t, J = 7.13, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 165.4, 165.1, 164.2, 144.5, 117.0, 81.7, 62.9, 62.7, 53.1, 14.2. Anal. Calcd for $C_{11}H_{12}Br_2O_6$: C, 33.03; H, 3.02; Br, 39.95. Found: C, 33.38; H, 2.75; Br, 39.61.

Diisopropyl 2-(3,4-Dichloro-5-oxo-2,5-dihydro-furan-2-yl)-malonate (15). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 5.55 (d, J = 4.10 Hz, 1H), 5.08 (m, 2H), 3.89 (d, J = 4.10 Hz, 1H), 1.25 (d, J = 6.25 Hz, 6H), 1.22 (m, 6H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 164.5, 163.8, 149.8, 122.8, 79.1, 70.9, 70.8, 53.2, 21.8, 21.7. Anal. Calcd for $C_{13}H_{16}Cl_2O_6$: C, 46.04; H, 4.75. Found: C, 45.79; H, 4.76.

Diisopropyl 2-(3,4-Dibromo-5-oxo-2,5-dihydro-furan-2-yl)-malonate (16). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 5.53 (d, J = 3.91 Hz, 1H), 5.10 (m, 1H), 5.03 (m, 1H), 3.90 (d, J = 3.91 Hz, 1H), 1.25 (d, J = 6.25 Hz, 6H), 1.22 (d, J = 6.25 Hz, 3H), 1.21 (d, J = 6.25 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 165.5, 164.7, 163.8, 144.8, 116.9, 81.8, 70.9, 70.6, 53.4, 21.7. Anal. Calcd for $C_{13}H_{16}Br_2O_6$: C, 36.48; H, 3.77; Br, 37.33. Found: C, 36.85; H, 3.71; Br, 37.31.

Benzyl Ethyl 2-(3,4-Dibromo-5-oxo-2,5-dihydro-furan-2-yl)-malonate (17). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.35 (m, 5H), 5.56 (m, 1H), 5.20 (m, 2H), 4.20 (m, 2H), 4.01 (d, J = 4.09 Hz, 1H), 1.24 (m, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 165.4, 165.0, 164.1, 144.6, 134.6, 129.1, 128.9, 128.7, 117.0, 81.7, 68.5, 68.3, 63.0, 62.8, 53.1, 52.9, 14.1. HRMS (ESI) calcd for $C_{16}H_{14}Br_2NaO_6$ 482.9055 ($M + Na^+$), found 482.9039.

Diethyl 2-(3,4-Dibromo-5-oxo-2,5-dihydro-furan-2-yl)-2-methyl-malonate (18). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 5.77 (s, 1H), 4.25 (m, 4H), 1.43 (s, 3H), 1.27 (t, J = 7.13 Hz, 6H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 167.6, 167.3, 165.3, 144.7, 116.8, 85.5, 63.0, 57.0, 15.3, 14.1. Anal. Calcd for $C_{12}H_{14}Br_2O_6$: C, 34.81; H, 3.41; Br, 38.60. Found: C, 34.54; H, 3.18; Br, 38.80.

(3,4-Dibromo-5-oxo-2,5-dihydro-furan-2-yl)-acetic Acid (19). ^{1}H NMR (400 MHz, DMSO-d_6) δ: 12.95 (br. s, 1H), 7.08 (s, 1H), 3.60 (s, 2H). ^{13}C NMR (100 MHz, DMSO-d_6) δ: 167.7, 165.9, 144.4, 118.5, 95.0, 41.7. IR (KBr): 2997, 2952, 1784, 1763, 1717 cm^{-1}. Anal. Calcd for $C_6H_4Br_2O_4$: C, 24.03; H, 1.34. Found: C, 24.65; H, 1.08.

2-(3,4-Dichloro-5-oxo-2,5-dihydro-furan-2-yl)-propionic Acid (20, diastereomeric mixture). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 10.41 (br s, 1H), 6.93 (d, J = 2.15 Hz, 90% of 1H), 6.91 (d, J = 3.71 Hz, 10% of 1H), 3.66−3.59 (m, 1H), 1.57 (d, J = 7. 23 Hz, 10% of 3H), 1.53 (d, J = 7.42 Hz, 90% of 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 174.6, 167.5, 147.0, 125.0, 91.8,

(19) Lattmann, E.; Kinchington, D.; Singh, H.; Merino, I.; Begum, A.; Ayuko, W. O.; Tisdale, M. J. *Pharm. Pharmacol. Lett.* **2001**, *11*, 5.

45.8, 13.5. LRMS (APCI) *m/z*: 224.9 $[M - 1]^-$. HRMS (ESI) calcd for $C_7H_4ClO_4$ 186.9798 ($[\{M - HCl\} - H]^-$), found 186.9794.

Octyl Cyano-(3,4-dibromo-5-oxo-2,5-dihydro-furan-2-yl)-acetate (21). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 5.54 (d, J = 2.54 Hz, 70% of 1H), 5.52 (d, J = 3.32 Hz, 30% of 1H), 4.30 (t, J = 6.84 Hz, 1H), 4.25 (m, 1H), 4.18 (m, 1H), 1.71 (m, 2H), 1.27 (m, 10H), 0.87 (br t, J = 8.0 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 164.2, 162.0, 161.4, 142.6, 118.4, 110.5, 81.1, 68.8, 68.6, 60.6, 41.2, 40.9, 31.9, 29.3, 28.5, 25.8, 22.8, 14.3. Anal. Calcd for $C_{15}H_{19}Br_2NO_4$: C, 41.21; H, 4.38; N, 3.20; Br, 36.56. Found: C, 41.32; H, 4.18; N, 3.16: Br, 36.79.

Ethyl 2-(3,4-Dichloro-5-oxo-2,5-dihydro-furan-2-yl)-malonamate (22, diastereomeric mixture). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 5.74 (d, J = 2.93 Hz, 60% of 1H), 5.67 (d, J = 3.91 Hz, 40% of 1H), 4.22 (m, 2H), 3.87 (d, J = 3.91 Hz, 40% of 1H), 3.80 (d, J = 3.13 Hz, 60% of 1H), 1.30 (t, J = 7.13 Hz, 40% of 3H), 1.22 (t, J = 7.13 Hz, 60% of 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 167.3, 166.5, 166.1, 64.8, 150.9, 150.6, 123.3, 80.0, 79.8, 63.3, 63.0, 52.6, 51.8, 14.0. Anal. Calcd for $C_9H_9Cl_2NO_5$: C, 38.32; H, 3.22; N, 4.97; Cl, 25.14. Found: C, 38.29; H, 3.08; N, 4.88; Cl, 24.99.

Ethyl (3,4-Dichloro-5-oxo-2,5-dihydro-furan-2-yl)-nitro-acetate (23, diastereomeric mixture). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 5.75 (d, J = 2.73 Hz, 60% of 1H), 5.71 (d, J = 4.09 Hz, 40% of 1H), 5.66 (d, J = 2.73 Hz, 60% of 1H), 5.55 (d, J = 4.29 Hz, 40% of 1H), 4.37 (m, 2H), 1.31 (m, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 163.5, 159.7, 151.9, 123.9, 101.1, 84.9, 64.8, 14.0. LRMS (APCI) *m/z*: 284.0 (M^-).

Acknowledgment. K.D.S. wishes to thank Pfizer, Inc. for a postdoctoral fellowship.

Supporting Information Available: ^{1}H and ^{13}C NMR data of the compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

JO050538T