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Efficient formation of novel and versatile building blocks from mucohalic acids: new substitute for tetronic acid and γ-alkylidenebutenolide

Ji Zhang,* Koushik Das Sarma and Timothy T. Curran

Chemical Research and Development, Pfizer Global Research and Development, Ann Arbor Laboratories, Pfizer, Inc., 2800 Plymouth Road, Ann Arbor, MI 48105, USA

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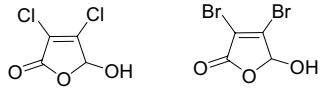
Abstract—Novel and useful building blocks were synthesized efficiently by DABCO mediated highly selective dehalogenation of Knoevenagel aldol adducts of mucochloric acid and mucobromic acid. These new compounds were found to undergo palladium catalyzed C–C bond forming reactions (Suzuki and Sonogashira cross-coupling) in high yields.

The abundance of a variety of biologically active γ-alkylidenebutenolides has attracted attention of synthetic chemists for many years.[1] Peridinin, a carotenoid of an auxiliary light-harvesting pigment for photosynthesis in the sea, causes red tides;[2] asparagamine A is an alkaloid from *Asparagus racemosus*, which reveals potent antioxytocin activity,[3] and lissoclinolide from *Lissoclinum patella* exhibits activity against the Gram-negative bacterium *Escherichia coli*.[4] Recently, the total synthesis of xerulinic acid, an intensely yellow pigment from the fungus *Xerula melanotricha*, that suppresses the biosynthesis of cholesterol through inhibition of HMG-CoA was reported.[5] Synthesis of halogenated γ-alkylidenebutenolide based natural product analogues with quorum sensing antagonist activities has also been explored.[6] Consequently, the search of versatile building blocks[7] and new synthetic methods[8] for the efficient construction of γ-alkylidenebutenolides and γ-butenolides (including γ-lactones) has been intensely investigated.[9] Although tetronic acid[10] was used widely in the building of butenolides via its triflate,[11] tosylate,[12] and bromide[13] under palladium catalyzed cross coupling, it has several disadvantages, including stability, equilibrium of enol and keto form, and the poor regioselectivity in the bromination. Herein, we report a new and useful equivalent for γ-alkylidenebutenolide and tetronic acid from inexpensive and often under-utilized mucohalic acids,[14] two old and fascinating molecules.[15]



Mucochloric acid **Mucobromic acid**

Hydrogenation of Knoevenagel adduct **1** derived from reaction of mucochloric acid with diethyl malonate[16] produced an open chain monoacid **3** as the exclusive product in excellent isolated yield (95%). Surprisingly, the desired γ-butanolide **2** could not be isolated under the reaction conditions (H_2, Pd/C, Et_3N at 40 psi in EtOH). The early rationalization was that presumably a conjugated diene **4** formed as an intermediate. Interestingly, when the Et_3N was added to **1** in THF, a pure product was isolated in 82% yield. MS showed this to be a molecule with only one Cl atom (a molecular ion of 275) and ^1H NMR showed the presence of one alkenic proton in the molecule. Based on the analytical data, the predicted structure was **5** or **6**, which was confirmed to be **5** by X-ray crystallographic analysis (Fig. 1).[17]

A plausible mechanism for the formation of this novel β-halo-γ-alkylidenebutenolide is shown in Scheme 1. In an effort to trap the intermediate **I**, a solution of NEt_3 in THF was added dropwise to a solution of **1**

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* Corresponding author. Tel.: +1 734 622 3940; fax: +1 734 622 3294; e-mail: ji.zhang@pfizer.com

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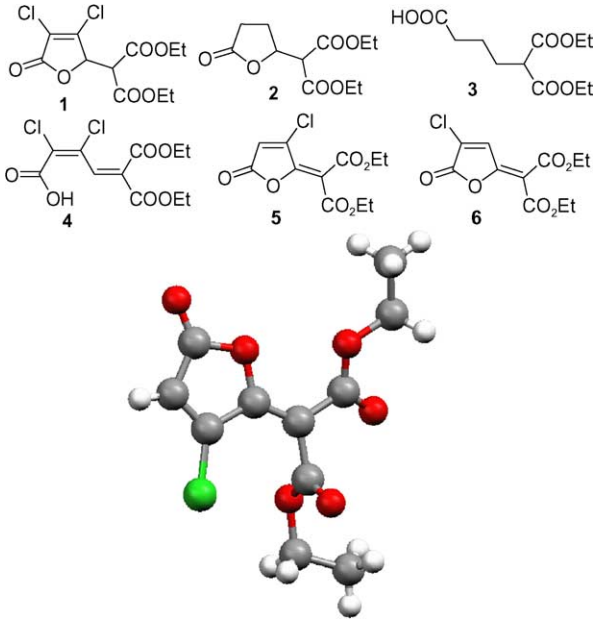
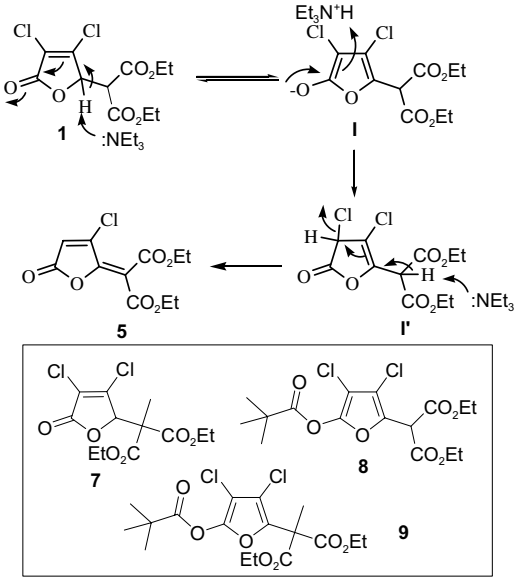


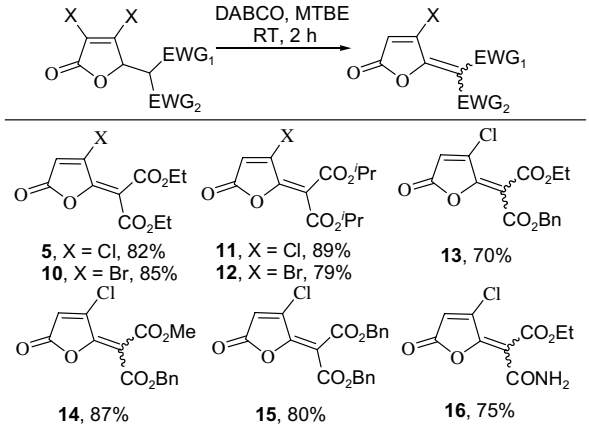
Figure 1. Knoevenagel aldol adduct, related compounds and X-ray crystal structure of **5**.



Scheme 1. Plausible mechanism and related compounds.

and pivaloyl chloride in THF. Though the presence of **8** could be seen by HPLC and by mass spectroscopy, it was found to revert back to **1** on silica and a mixture of **1** and **5** was obtained upon column purification. The Knoevenagel aldol adduct **7**, however, offers a unique possibility of trapping the intermediate **I**. Indeed, when NEt_3 was added to a pre-stirred solution of **7** and pivaloyl chloride in MeCN, the ester **9** was isolated in 60% yield.[18]

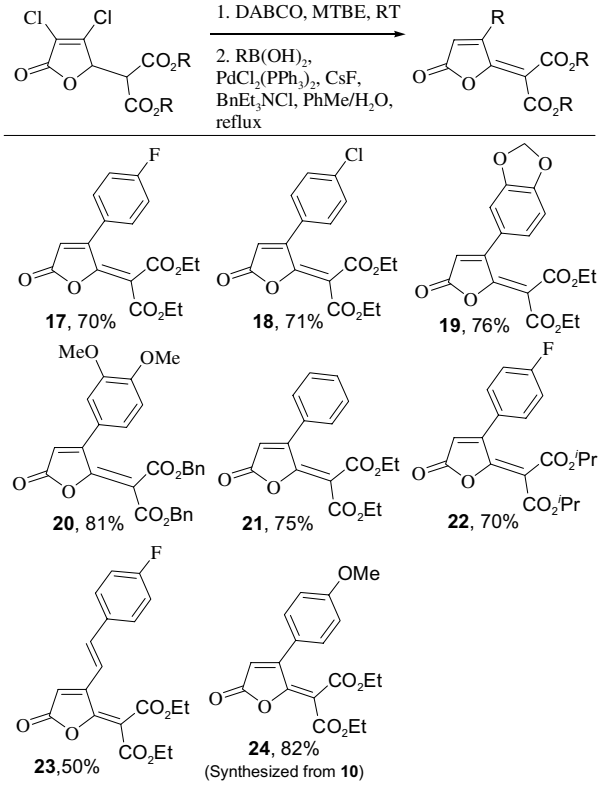
A series of new β-halo-γ-alkylidenebutenolides were prepared using these mild and facile conditions (Scheme 2). NEt_3 was found to result in dark coloration of the reaction mixture and was replaced by DABCO as base. For



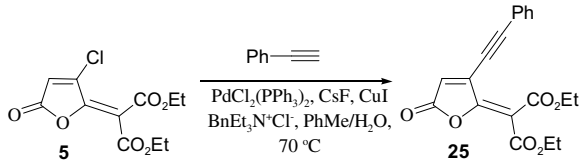
Scheme 2. β-Halo-γ-alkylidenebutenolides synthesized from α,β-dihalobutenolides.

an easy separation of the DABCO salt, the reaction was performed in *tert*-butylmethyl ether with 10–20% THF. In the literature, β-halo-γ-alkylidenebutenolides are generally synthesized from dibromolevulinic acid,[19] γ-monosubstituted allenic esters,[20] α-(1-hydroxyalkyl)- and α-(1-alkoxyalkyl)-α,β-unsaturated esters,[21] and 4-acylmethyl-2-chloro-4-hydroxy-2-cyclobutenones.[22] However, unlike the present methodology, all these methodologies are either lengthy or use corrosive reagents like oleum and bromine.

These novel β-halo-γ-alkylidenebutenolides turned out to be useful building blocks for Pd-catalyzed C–C bond



Scheme 3. Synthesis of Suzuki products from α,β-dihalobutenolides.



Scheme 4. Sonogashira product from β-halo-γ-alkylidenebutenolides.

formation reactions. The Suzuki coupling with an aryl boronic acid worked without using any special ligand or harsh conditions (Scheme 3).[23] Though reported procedures use a bromide in most cases, both Cl- and Br-derivatives worked equally well in this case. Similarly a Sonogashira coupling between **5** and phenyl acetylene resulted in the isolation of **25** in 70% isolated yield (Scheme 4).

In conclusion, the selective manipulation of highly functionalized mucohalic acids into novel and useful β-halo-γ-alkylidenebutenolides building blocks was discovered. These compounds were found to undergo palladium catalyzed C–C bond forming reactions in high yields. The present methodology offers a simple, efficient, and highly practical alternative for synthesizing γ-alkylidenebutenolides and tetronic acid derivatives starting from mucohalic acids. Further utilization of these versatile building blocks in organic synthesis will be reported in due course.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2005.07.123.

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17. Crystal data was collected on a Bruker AXS Apex CCD using graphite monochromated Mo Kα radiation ($\lambda = 0.71073$ Å). The structures were solved with direct methods and refined by full-matrix least squares against F^2 using the SHELXTL program. Crystal data for **5**: $C_{11}H_{11}ClO_6$, triclinic, space group *P*-1, $a = 8.417(3)$, $b = 8.982(3)$, $c = 10.254(4)$, $\alpha = 70.426(5)$, $\beta = 68.827(5)$, $\gamma = 62.193(5)°$, $V = 625.8(4)$ Å^3, $Z = 2$, ρ calcd $= 1.458$ mg m^{-3}, $T = 298$ K, $2\theta\max = 28°$, $\mu = 0.322$ mm^{-1}, 5634 reflections

measured, of which 2855 were unique ($R_{int} = 0.0196$) R indices: $R1 = 0.0442$, ($I > 2\sigma(I)$), $wR2 = 0.1089$ (all data).
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