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# Facile Syntheses of 2,2-Dimethyl-6-(2-oxoalkyl)-1,3-dioxin-4-ones and the Corresponding 6-Substituted 4-Hydroxy-2-pyrones

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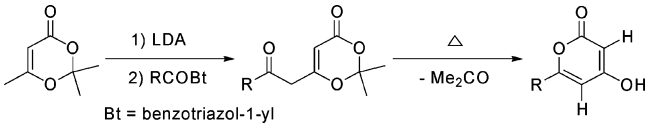
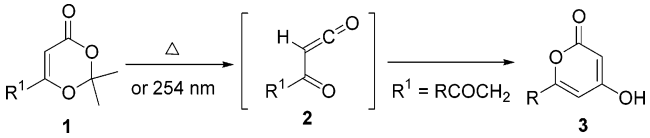



A variety of 2,2-dimethyl-6-(2-oxoalkyl)-1,3-dioxin-4-ones **5a**−***l*** and the corresponding 6-substituted 4-hydroxy-2-pyrones **3a**−***l*** were prepared in high yields under mild reaction conditions by the reaction of 2,2,6-trimethyl-1,3-dioxin-4-one **4** with 1-acylbenzotriazoles **9** in the presence of LDA followed by thermal cyclization of **5a**−***l*** to **3a**−***l***. Synthesis of novel 6-(1-benzoylalkyl)-2,2-dimethyl-1,3-dioxin-4-ones **12a**−**c** was achieved by alkylation of dioxinone **5a** and their subsequent cyclization gave 5-alkyl-4-hydroxy-2-pyrones **13a**−**c**.

2-Pyrones represent an important class of lactones that are substructures of many natural products[1] showing a wide range of biological activity, such as potent nonpeptidic HIV protease inhibitory,[2] antimicrobial,[3] androgen-like,[4] antifungal,[5] and pheromonal[6] effects. Although 2-pyrones have been known for more than 100 years, due to their inaccessibility, studies before the 1960s were limited to a small group of 6-unsubstituted 2-pyrones. Over recent decades the chemistry of 6-unsubstituted 2-pyrones has been investigated intensively and has led to the development of 2-pyrone chemistry.[7]

**SCHEME 1**




By contrast, relatively few examples of the preparation of 6-substituted 2-pyrones have been reported. 1,3-Dioxin-4-ones including 2,2-dimethyl-6-(2-oxoalkyl)-1,3-dioxin-4-ones are versatile synthons which can be prepared with a variety of substitution patterns. Facile ring opening of dioxinone **1** to acylketene **2** under either thermal or photochemical conditions allows cyclization to 6-substituted-4-hydroxy-2-pyrones **3** (Scheme 1). Traditionally, the synthesis of 2,2-dimethyl-6-(2-oxoalkyl)-1,3-dioxin-4-ones **5** has been accomplished either by electrophilic addition of acyl halides or anhydrides to the $\gamma$-position of the lithium enolate of **4** (38% to 69% yields),[8,9] or by a two-step procedure involving vinylogous Mukaiyama aldol addition of (2,2-dimethyl-6-methylene-6*H*-1,3-dioxin-4-yloxy)trimethylsilane **6** to aldehydes to give alcohols **7**, followed by oxidation of the latter to give **5** using the Dess−Martin method. Ketones **5** then underwent thermal cyclization to give 6-substituted-4-hydroxy-2-pyrones **3** (Scheme 2).[8,10]

Problems with handling and storing acyl halides, and their incompatibility with acid-sensitive functional groups, prompted our search for alternatives.[11] Benzotriazole acts as a good leaving group and has been employed extensively as a synthetic auxiliary.[12] 1-Acylbenzotriazoles are advantageous carboxylic acid derivatives in that they are stable and readily prepared in one step from carboxylic acids even in cases where an acid-sensitive functionality is present.[13] They have been widely used in many N-,[13b,14] C-,[15] O-,[15d,16] and S-acylation reactions.[17]

We now describe the facile syntheses of 2,2-dimethyl-6-(2-oxoalkyl)-1,3-dioxin-4-ones **5** and the corresponding

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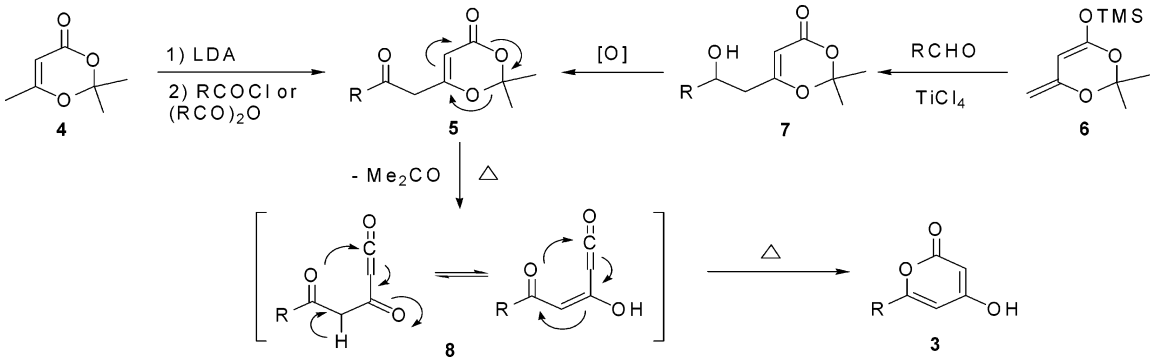
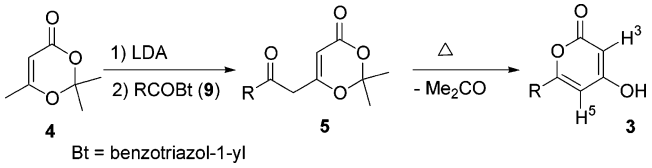
**SCHEME 2**




**SCHEME 3**




2-pyrones **3** by a selective vinylogous addition process of 1-acylbenzotriazoles **9** to the $\gamma$-position of the lithium enolate of **4**, followed by thermal cyclization by heating under reflux in toluene.

**Results and Discussion.** 1-Acylbenzotriazoles **9a**−**n** were readily prepared by treating the corresponding carboxylic acids either (i) with thionyl chloride and benzotriazole in methylene chloride at 25 °C[13c] or (ii) in THF with 1-(methylsulfonyl)-1*H*-1,2,3-benzotriazole in the presence of triethylamine under reflux overnight.[13b]

Treatment of dioxinone **4** with 1.3 equiv of LDA (prepared in situ at −78 °C) resulted in formation of the dark brown lithium enolate of **4**. Subsequent reaction with 1-acylbenzotriazoles **9a**−***l*** between −78 °C and ambient temperature overnight yielded 2,2-dimethyl-6-(2-oxoalkyl)-1,3-dioxin-4-ones **5a**−***l*** in 37−66% yields (Scheme 3 and Table 1). The structures of **5a**−***l*** were supported by $^1$H and $^{13}$C NMR data (see the Supporting Information).

Heating solutions of **5a**−***l*** in toluene under reflux for 20−30 min produced 4-hydroxy-6-substituted-2-pyrones **3a**−***l*** in 53−86% yields (Scheme 3 and Table 1). The structures of **3a**−***l*** were supported by $^1$H and $^{13}$C NMR data (see the Supporting Information). In a NOE experiment on **3e** irradiation of the OH signal at C-4 enhanced both H$^3$ and H$^5$ of the pyrone ring, thus offering an unequivocal confirmation of the 2-pyrone structure in accord with previous studies.[2d,18] gHMBC spectra on **3e** show 3-bond coupling of H-1 and H-3 of the naphthalene ring with C-6 of the pyrone ring, and 2-bond coupling of H$^3$ and H$^5$ with C-4 and 2-bond coupling of H$^3$ with C-2 of the pyrone ring, thus confirming the assignment of C-2 at 163.1 ppm and C-4 at 170.6 ppm.

**TABLE 1. Preparation of 1,3-Dioxin-4-ones 5 and 2-Pyrones 3**

| entry | R (**9**: RCOBt) | **5**, yield % | **3**, yield % | ref |
|---|---|---|---|---|
| **a** | Ph | 65 | 82 | 8 |
| **b** | 4-Me$C_6H_4$ | 58 | 77 | 19 |
| **c** | 4-Cl$C_6H_4$ | 61 | 75 | 20 |
| **d** | $Ph_2CH$ | 58 | 85 | |
| **e** | $\beta$-Naphthyl | 65 | 66[b] | |
| **f** | $n$-$C_6H_{13}$ | 53 | 70 | |
| **g** | $^t$Bu | 52 | 86 | |
| **h** | $^i$Pr | 51 | 53 | |
| **i** | $CH_2$=CH−$(CH_2)_8$ | 51 | 64 | |
| **j** | PhCH=CH | 37[a] | 73 | 10a |
| **k** | 2-Furyl | 66 | 61 | 10a |
| ***l*** | 2-Thienyl | 60 | 82 | |

[a] Byproduct *N*,*N*-diisopropyl-3-phenyl-3-(2,2,6-trimethyl-4-oxo-4*H*-1,3-dioxin-5-yl)propanamide (**b1**) was isolated in 21% yield. [b] Byproduct (*Z*)-4-hydroxy-4-(2-naphthyl)-3-buten-2-one (**b2**) was isolated in 14% yield.

A limitation to the above method was found when 1-(1*H*-1,2,3-benzotriazol-1-yl)-2-[1,1′-biphenyl]-4-yl-1-ethanone **9m** and 1-(1*H*-1,2,3-benzotriazol-1-yl)-2-(phenylsulfanyl)-1-ethanone **9n** were employed as electrophiles in the reaction. Neither of the desired 2-pyrones **5m** or **5n** was detected in the corresponding reaction mixtures, but instead, *N*,*N*-diisopropylacetamides **10m** and **10n** were isolated as the major products in 37% and 41% yields, respectively, together with some unreacted dioxinone **4** (Scheme 4). The mechanism for the formation of **10m**,**n** is presumably as shown in Scheme 5. Due to the existence of active α-hydrogens in 1-acylbenzotriazoles **9m**,**n**, anion exchange occurs between the anion of **4** and **9m**,**n** to give ketenes **11m**,**n**, which then add to *N*,*N*-diisopropylamine to yield acetamides **10m** and **10n**. Interestingly, the same reaction was not detected when

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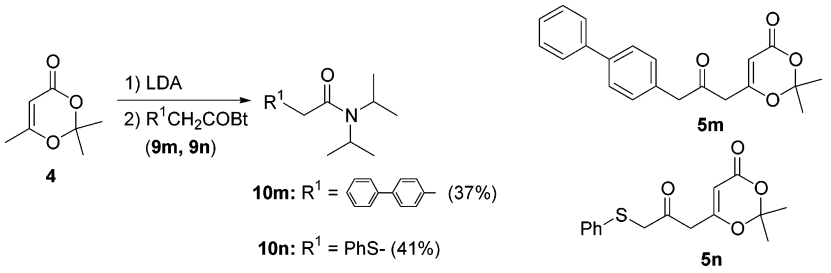
**SCHEME 4**

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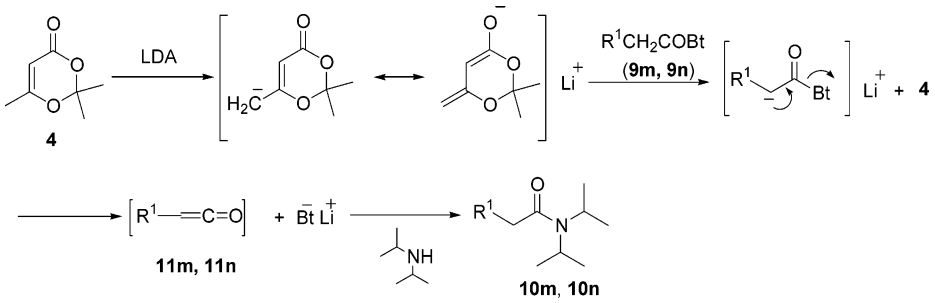


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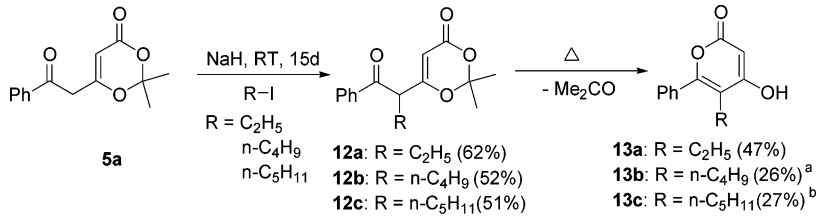


[a] Byproduct 2-butyl-1-phenyl-1,3-butanedione (**b3**) was isolated in 15% yield. [b]Byproduct 2-pentyl-1-phenyl-1,3-butanedione (**b4**) was isolated in 22% yield.

1-acylbenzotriazole **9d** was reacted with 1,3-dioxin-4-one **4**, even though **9d** has a more acidic α-hydrogen. Presumably steric hindrance by the two phenyl groups in **9d** prevents the anion exchange reaction.

Alkylation of dioxinone **5a** was achieved by reactions with alkyl iodides in THF in the presence of sodium hydride, which led to novel products **12a**−**c** in 51−62% yields (Scheme 6). Transformations analogous to those described in Scheme 3 also succeeded with **12a**−**c** to give 5-alkylated 2-pyrone **13a**−**c** in 26−47% yields. The structures of **12a**−**c** and **13a**−**c** were supported by $^1$H and $^{13}$C NMR data (see the Supporting Information).

In conclusion, the facile synthesis described herein affords a general and versatile approach to the biologically important class of 2-pyrones. The present method provides a complementary approach to earlier methods, specifically those where acid chlorides are employed. The advantage of this method includes the following: (i) most acylbenzotriazoles are stable to storage over months under ambient conditions, (ii) they are sufficiently reactive to form new C−C bonds between −78 °C and ambient temperature, but stable enough to resist side reactions, and (iii) the intermediate 1,3-dioxin-4-ones are obtained in good yields compared with those using the acid chloride method.

## Experimental Section

**General Methods and Materials.** Melting points were determined on a hot-stage apparatus and are uncorrected. NMR spectra were recorded in $CDCl_3$ or DMSO-$d_6$ with TMS as the internal standard for $^1$H (300 MHz) or $CDCl_3$ or DMSO-$d_6$ as the internal standard for $^{13}$C (75 MHz), unless otherwise specified. All reactions were carried out under an atmosphere of nitrogen. Anhydrous THF was obtained by distillation from sodium/benzophenone ketyl immediately prior to use. Column chromatography was performed with S733-1 silica gel (200−425 mesh).

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**Supporting Information Available:** Characterization data for compounds **5a**−***l***, **b1**; **3a**−***l***, **b2**; **10m**,**n**; **12a**−**c**; and **13a**−**c**, **b3**,**4**. This material is available free of charge via the Internet at http://pubs.acs.org.

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