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The Chemistry of Vicinal Tricarbonyls.
A New Synthesis of Substituted Furans.

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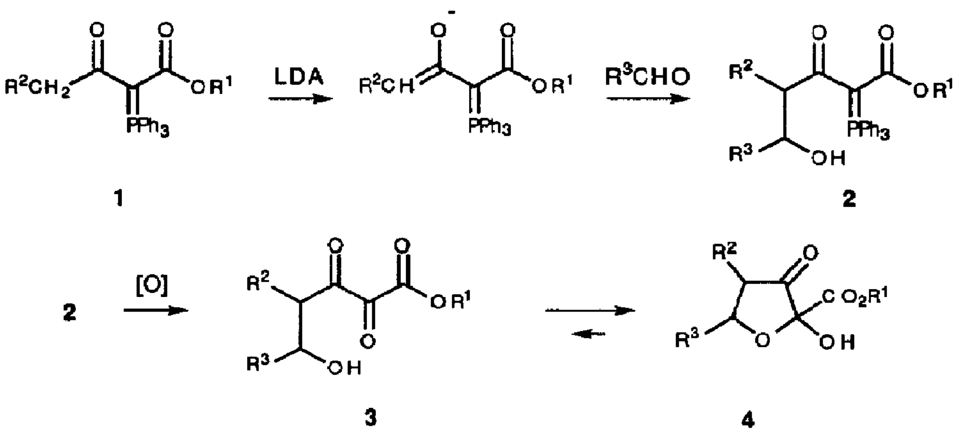
Abstract: Enolates of acyl phosphoranylidine carboxylates react with aldehydes to form secondary alcohols which undergo intramolecular addition to the central carbonyl of a vicinal tricarbonyl unit, generated in a separate step. The resulting dihydrofuranols undergo acid-catalyzed dehydration to form 3-hydroxyfuran-2-carboxylates.

The highly electrophilic nature of the central carbonyl in vicinal tricarbonyls has been recognized for some time, but, until recently, little attention has been given to the use of this system in synthesis.[1] In earlier work, we used tricarbonyls in the formation of fused ring β-lactams,[2] as well as alkaloids in the vincamine,[3] isoquinoline,[4] prodigiosin,[5] and erythrina[6] families. In other work, the di- and trielectrophilic nature of a vinyl tricarbonyl unit has been exploited in the synthesis of 3-hydroxypyrrole-2-carboxylates and polycyclic indole derivatives from tryptamine.[7,8]

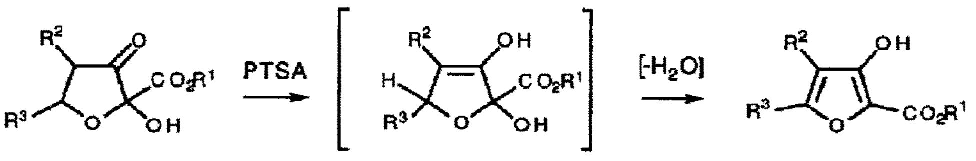
In our further studies on the chemistry of tricarbonyls, we have developed a novel route to substituted furans, heterocyclic systems which continue to attract attention in connection with their occurrence in products of biological interest. Our methodology makes use of the earlier findings of Cooke on the deprotonation of acyl phosphoranes of type **1** to form enolate anions[9] which take part in Michael addition reactions. In the present work (Scheme 1, no stereochemistry implied), we have allowed these anions to undergo aldol addition to a series of aldehydes, producing secondary alcohols **2**. In the next step, the phosphoranylidine group in **2** is cleaved oxidatively forming the tricarbonyl derivative **3** which acts as an acceptor for intramolecular addition of the alcohol group.[10] The resulting 4,5-dihydrofuranones **4**, isolated as a mixture of diastereomers, may then be dehydrated to produce the furan derivative **5**.

Scheme 1



1 2 3 4

Scheme 2



4 R^1 = Me **5**

In a typical experiment, the acyl phosphoranylidine **1**^{12} was deprotonated with 1.1 equiv of LDA or BuLi in THF at -5°C, followed by the addition of the aldehyde at -78°C. Gradual warming of the reaction mixture to -20°C produced the aldol products **2** in generally high yields. Subsequent oxidative cleavage of **2** was accomplished by ozone at -78°C, or Oxone®, at room temperature. The resulting β-hydroxy tricarbonyls **3** (not isolated) underwent immediate cyclization to the substituted dihydrofuranones **4** as evidenced by the IR spectra of the reaction products showing the expected carbonyl absorptions at 1770 and 1750 cm^{-1}, along with other spectroscopic and analytical data.^{14} Table 1 lists the yields of products **2** and **4** prepared in this way.

Table 1. Secondary Alcohols (**2**) from Condensation of **1** with Aldehydes (R^{3}CHO). Dihydrofuranones (**4**) Formed after Oxidation of **2** to Tricarbonyl (**3**).

Entry	R^1	R^2	R^3	**2** (% yield)^{14}	**4** (%yield)^{14}
a	Me	H	Ph	76	95 (88)^{11}
b	Me	H	Et	78	88
c	Me	H	n-Pentyl	67	93
d	Me	H	i-Butyl	74	90
e	Me	H	n-Hexyl	32	76
f	Me	H	t-Butyl	79	90
g	Me	H	i-Propyl	95	85
h	Me	Me	Ph	87^{11}	93
i	Me	Me	n-Hexyl	93^{11}	68
j	t-Butyl	H	Et	30	83
k	t-Butyl	H	Ph	84^{11}	75

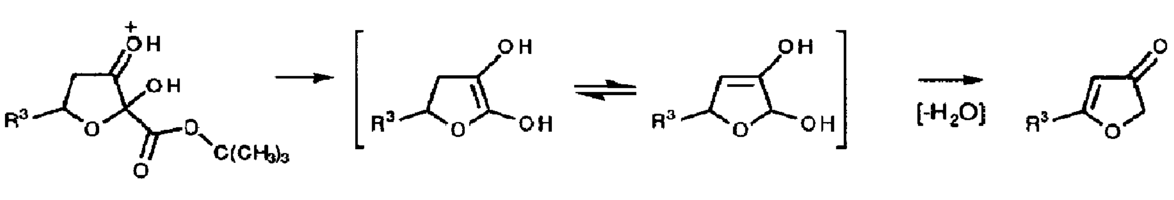
In contrast to the hydroxypyrrolidone carboxylates which undergo ready conversion to pyrrole derivatives with silica gel,^{7b} the dihydrofuranone counterparts were relatively resistant to dehydration with mild acids, remaining unaffected or giving poor results with acidic reagents such as $ZnCl_2$, P_2O_5, $SnCl_4$ and BF_3. It was found, however, that p-toluenesulfonic acid was a most effective catalyst for the conversion of 4, R^1=CH_3 to the furan system (Scheme 2). The isolated yields of 3-furanols **5** by this method^{13} were between 70 and 93% (Table 2).

Table 2. Conversion of Dihydrofuranones (**4**, R^1=CH_3) to Furane Derivatives (**5**).[14]

Entry	R^3	R^2	**5** (% yield)
a	Ph	H	87
b	Et	H	70
c	n-Pentyl	H	92
d	i-Butyl	H	75
e	n-Hexyl	H	84
f	t-Butyl	H	92
g	i-Propyl	H	88
h	Ph	Me	93
i	n-Hexyl	Me	93

Furan formation from the dihydro derivatives **4** was effective in the case of the methyl esters. With the t-butyl esters, decarboxylation appeared to take place readily before dehydration, yielding 3-(2H)-furanones. Thus, treatment of **4**, R^1=t-Bu, R^2=H, R^3=Et or Ph with $BF_3 \cdot Et_2O$ yielded **6**, most probably by the decarboxylation process shown in Scheme 3.

Scheme 3



4 **6**

In summary, we have demonstrated an efficient route to substituted 3-furanol-2-carboxylates, which should have general applicability in the synthesis of these heterocyclic systems.

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10. In these reactions, the ylide function may be viewed as a protecting group for the labile tricarbonyl aggregate.
11. n-Butyllithium (1.1 equiv) was used in place of LDA.
12. Phosphoranylidines **1** were prepared by addition of acetyl chloride or propionyl chloride to 2 equiv. of methyl or t-butyl (triphenylphosphoranylidine) acetate in benzene at 5°C.
13. Typically, 0.5 mmole of dihydrofuranone **4** and 10 mole % of PTSA in 15 mL of benzene was heated to reflux for 12 h. in a flask fitted with a Dean-Stark trap. The solvent was evaporated, the residue diluted with ethyl acetate, and washed with aq. $NaHCO_3$ and brine. The organic layer was dried, evaporated and distilled (bulb-to-bulb) to give the 3-furanol-2-carboxylates **5**.
14. Satisfactory spectroscopic data (^{1}H NMR, IR, HRMS) and/or C and H analyses were obtained for all new compounds, except as follows: HRMS were not obtained for entries **j**, Table 1 and **a**, **b** & **d**, Table 2. For the relatively labile compounds **4**, which appeared to predominate in an equilibrium with **3**, we obtained ^{1}H NMR and IR data only.

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