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An efficient methodology to substituted furans via oxidation of functionalized α-diazo-β-ketoacetates

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Dedicated to Harry Wasserman on the occasion of his 90th birthday

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ABSTRACT

DMDO oxidation of functionalized α-diazo-β-ketoacetates, formed by zinc triflate catalyzed Mukaiyama-aldol condensation of methyl diazoacetoacetate with aldehydes, occurred in quantitative yield to form dihydrofuranols that undergo acid catalyzed dehydration under mild conditions to generate 3-methoxy-furan-2-carboxylates in good yield.

1. Introduction

The vicinal tricarbonyl (VTC) moiety is an important functional unit in organic synthesis. This is mainly due to the highly electrophilic nature of the central carbonyl carbon, which can undergo bond formation with a variety of nucleophiles.[1] The first VTC compound was synthesized in 1890,[2] and since then there have been a large number of methods developed for their preparation.[3] In what have been an insightful contributions to the synthetic developments that utilize this chemistry, Wasserman and coworkers demonstrated multiple applications of the VTC system in the synthesis of β-lactams,[4] alkaloids,[5] pyrroles,[6] and indolizidines.[7]

In one application Wasserman used VTC compounds in a novel synthetic route directed to the synthesis of substituted furans (Scheme 1, Eq. 1),[8] an important class of compounds due to their abundance in natural products and biologically relevant molecules. In this methodology, the VTC unit was prepared by oxidation of phosphorus ylides that were synthesized from enolates of acyl phosphoranylidine carboxylates. Subsequent dehydration using PTSA yielded 3-hydroxy-furan-2-carboxylates in moderate yields. Herein, we report an improved approach for the synthesis of substituted furans that utilize the oxidation of functionalized α-diazo-β-acetoacetates, formed by zinc triflate catalyzed Mukaiyama-aldol condensation of alkyl diazoacetoacetates with aldehydes,[9] to generate VTC systems using dimethyldioxirane (DMDO) (Scheme 1, Eq. 2).

The advantages of this procedure are the ease of preparation and handling of the diazoacetoacetate reactants, the quantitative oxidation under neutral conditions, and the conversion of the VTC compounds to alkoxy-furans under mild conditions.

2. Results and discussion

Our synthesis begins with commercially available aldehydes **A** and methyl α-diazoacetoacetate **B** that is easily prepared by diazo transfer to methyl acetoacetate.[10] α-Diazoacetoacetates that include **B** are stable under a wide range of conditions.[11] TBSO-functionalized α-diazo-β-ketodicarbonyl compounds **1** were obtained by a convenient one-pot Mukaiyama-aldol reaction of aldehydes **A** and methyl α-diazoacetoacetate **B** in high yield (Scheme 2).[9] The TBSO-functionalized condensation products (**1**) were easily hydrolyzed with 4 N HCl in THF to form the corresponding alcohol products **2** in high yields (Table 1).

With a variety of functionalized α-diazo-β-ketodicarbonyl **2** in hand, we next sought to oxidize the diazo group to a carbonyl group. We initially began with *t*-butyl hypochlorite as an oxidant, since several reports have shown that *t*-butyl hypochlorite can generate VTC compounds from α-diazo-β-dicarbonyl compounds.[12] In our hands, however, the use of *t*-butyl hypochlorite afforded the desired product in moderate yield along with other unidentified by-products. As Saba reported that α-diazo-β-dicarbonyl compounds were oxidized to VTC derivatives using dimethyldioxirane (DMDO) in high yield,[13] we subjected diazo substrates **2** to DMDO.[14] This process resulted in the quantitative oxidation of the full range of diazo compounds **2**. The oxidized

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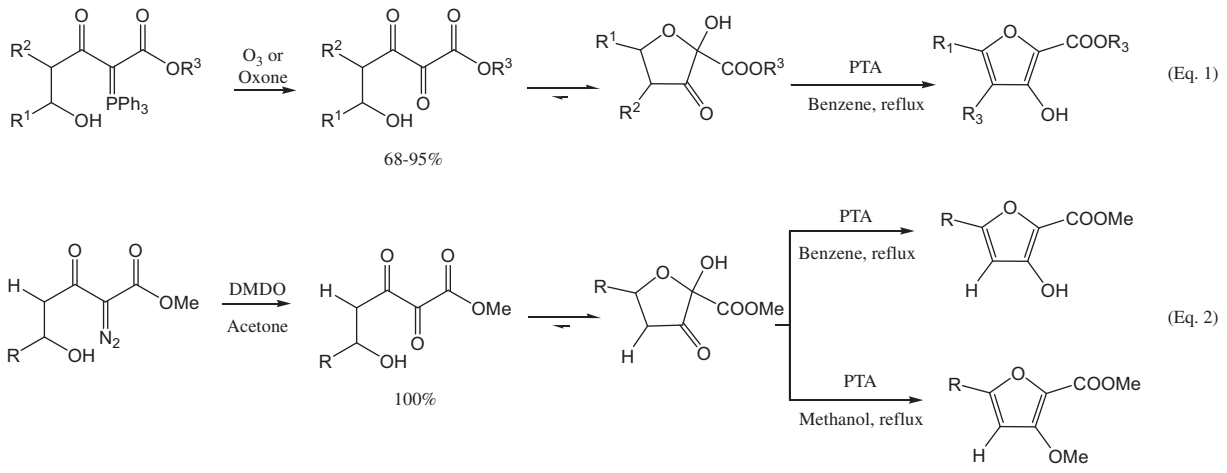
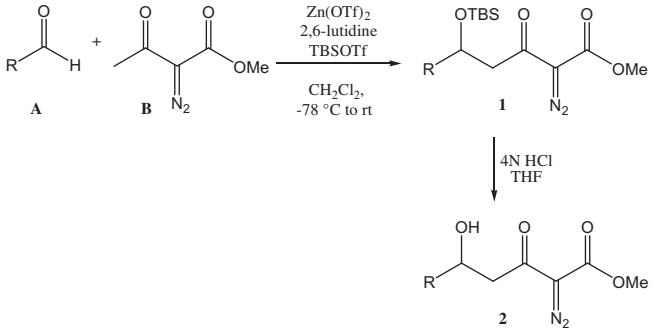


Scheme 1.



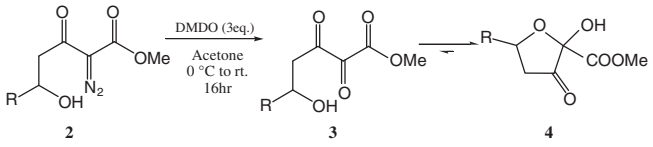
Scheme 2.

Table 1
Hydrolysis of compound **1** via Scheme 2[a]

Entry	R	Product	Yield[b] (%)
1	*n*-Heptyl	**2a**	90
2	*t*-Butyl	**2b**	90
3	C_6H_5	**2c**	95
4	2-$NO_2C_6H_4$	**2d**	91
5	4-$NO_2C_6H_4$	**2e**	92
6	4-ClC_6H_4	**2f**	88
7	3,5-$(CH_3)_2C_6H_3$	**2g**	93
8	2,4,6-$(CH_3)_3C_6H_2$	**2h**	85
9	2-Napthyl	**2i**	95

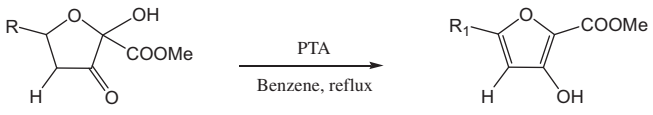
[a] Reaction performed in THF at room temperature using 4 N HCl for hydrolysis.
[b] Isolated yield.

Table 2
Oxidation of α-diazoacetoacetates **2** to a vicinal tricarbonyl with DMDO[a]



Entry	R	Product[b]	dr[c]
1	*n*-Heptyl	**4a**	33:67
2	*t*-Butyl	**4b**	26:74
3	C_6H_5	**4c**	30:70
4	2-$NO_2C_6H_4$	**4d**	36:64
5	4-$NO_2C_6H_4$	**4e**	35:65
6	4-ClC_6H_4	**4f**	34:66
7	3,5-$(CH_3)_2C_6H_3$	**4g**	32:68
8	1,4,6-$(CH_3)_3C_6H_2$	**4h**	15:85
9	2-Napthyl	**4i**	29:71

[a] Reaction performed in acetone at 0 °C with dimethyldioxirane as oxidant.
[b] Quantative yield of products **4** were obtained.
[c] Determined by ^{1}H NMR of the crude product **4**.



Isolated Yield (%)
R = C_6H_5 51
R = 2-NO_2-C_6H_4 40

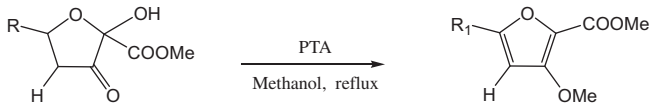
Scheme 3.

compounds **3** are in equilibrium with dihydrofuranols **4** (Table 2) and existed as a mixture of diastereomers. The diastereomer ratios of **4**, obtained from their ^{1}H NMR spectra, were approximately 1:2 for most of the compounds. Compound **4h** had the highest dr ratio (1:5.6) due to the steric effect mesityl group. Compounds **4** were easily isolated by evaporation of acetone and taken to the next step without further purification.

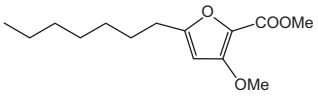
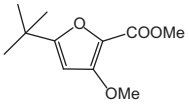
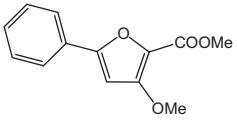
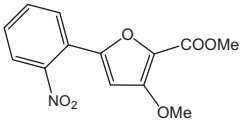
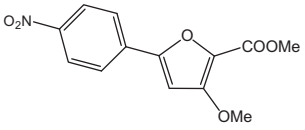
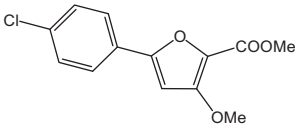
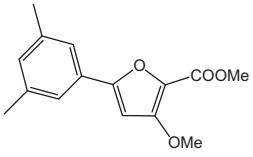
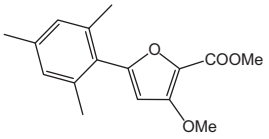
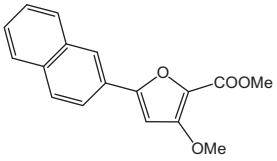
The hemiketal form of furanone **4** then underwent acid catalyzed dehydration to form 3-hydroxyfuran-2-carboxylates **5** (Scheme 3) by the same procedure as that employed by Wasserman and Lee.[8] However, reactions in refluxing benzene together with catalytic PTSA resulted in product decomposition, and isolation of **5** by silica gel chromatography occurred in a relatively low yield. However, changing the reaction solvent to methanol resulted in the expected conversion of hemiketal **4** to 3-methoxyfuran-2-carboxylates **6** (Table 3). This modification also allowed for ease in purification since the 3-hydroxyfuran-2-carboxylates **5** were otherwise difficult to purify.

A proposed mechanism for the formation of 3-methoxyfuran-2-carboxylates **6** is given in Scheme 4. Hemiketal formation at position 3 is proposed to precede formation of vinyl ether A, which

Table 3
Acid catalyzed dehydration for the synthesis of 3-methoxy-2-carboxylate furans[a]



4 **6**

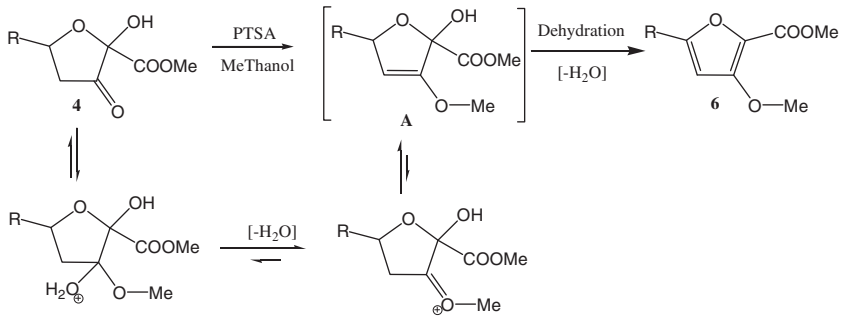
Entry	R	Product		Yield[b] (%)
1	*n*-Heptyl		**6a**	90
2	*t*-Butyl		**6b**	91
3	C_6H_5		**6c**	80
4	2-NO_2-C_6H_4		**6d**	86
5	4-NO_2-C_6H_4		**6e**	92
6	4-Cl-C_6H_4		**6f**	75
7	3,5-$(CH_3)_2$-C_6H_3		**6g**	75
8	1,4,6-$(CH_3)_3$-C_6H_2		**6h**	60[c]
9	2-Napthyl		**6i**	85

[a] Reaction was refluxed in methanol with *p*-toluenesulfonic acid monohydrate (PTSA) overnight.
[b] Isolated yield.
[c] Combined yield of product and impurity from reaction mixture, which is unable to be separated by general silica gel chromatography.

subsequently undergoes acid catalyzed dehydration to generate furan **6**. By replacing methanol with a different alcohol, the potential for further modifications in product formation at position 3 is suggested in this mechanism.

3. Conclusion

In summary, we have developed an efficient method for the synthesis of 3-methoxyfuran-2-carboxylates and developed an



Scheme 4. Proposed mechanism.

improved methodology for the preparation of 3-hydroxyfuran-2-carboxylates. We also have opened up the possibility of derivatization at C3 position by the use of different nucleophile. Application of this methodology is currently on the way for preparing the side chain of roseophilin.

Acknowledgments

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Supplementary data

Supplementary data (general synthetic methods, HRMS, ^{1}H and ^{13}C NMR of reaction products) associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2010.11.166.

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