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An easy approach to dihydrofurans by one-step cyclisation of 2-alkenyl substituted 1,3-dicarbonyl compounds

Roberto Antonioletti,* Giuliana Righi, Lia Oliveri and Paolo Bovicelli

Centro CNR di Studio per la Chimica delle Sostanze Organiche Naturali, Dipartimento di Chimica, Università 'La Sapienza', P. le A. Moro, Box 34 Roma 62, 5-00185 Rome, Italy

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Abstract

Dihydrofuran derivatives were obtained by a simple one-step procedure involving an easy epoxidation of 2-alkenyl-1,3-dicarbonyl compounds by dimethyldioxirane prepared in situ and a subsequent cyclisation under the same basic reaction conditions. © 2000 Published by Elsevier Science Ltd.

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In previous work we described cyclisations of γ,δ-unsaturated ketones to obtain dihalodihydropyrans[1] and 2-alkenyl substituted 1,3-dicarbonyl compounds in a convenient approach to furan derivatives.[2]

Cyclic ethers are often present in naturally occurring compounds[3] and furthermore are useful synthetic intermediates;[4] for these reasons new methodologies for their preparation have been intensively studied during the last few years.[5]

Our approach to the synthesis of furan and dihydrofuran derivatives involves the utilisation of 1,3-dicarbonyl compounds as a source of an intramolecular nucleophile and iodine as an electrophile to promote a cyclisation reaction. In this way, dihydrofurans functionalised with an iodine atom in the side-chain can be obtained in highly regio- and diastereo-selective processes.[6]

Due to our interest in methods for the synthesis of dihydrofuran derivatives, we explored the possibility of using an oxirane as the electrophile. The use of dioxiranes, which are a new generation of epoxidising reagents studied in our laboratories in the last decade,[7] could, in this case, allow a one-pot transformation.

Substrates taken as models for this study were 2-alkenyl-1,3-dicarbonyl compounds, of which we have had experience of preparing.[8]

* Corresponding author.

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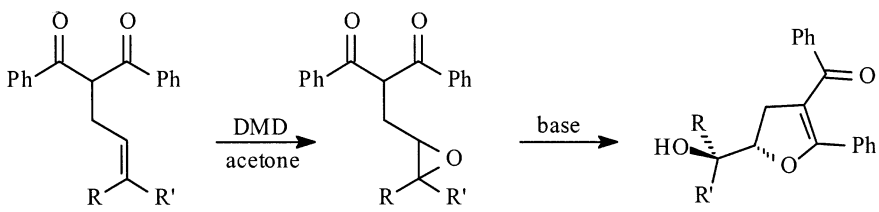
The epoxides were submitted to different reaction conditions to allow intramolecular nucleophilic attack. The reactions worked well to give the dihydrofuran derivatives **3** with complete regiochemical control, the 5-*exo*-tet cyclisation being the only observed process.[9] In contrast, the cyclisation of **1c** using iodine as the electrophile gave a mixture of dihydropyran and dihydrofuran derivatives. As shown in Table 1, the use of a base (NaH or Na_2CO_3) on the isolated epoxides, or the addition of a base (Na_2CO_3) to the reaction mixture led to similar results. Epoxides **2** were prepared by the use of dimethyldioxirane (DMD) in a quantitative process.

We then optimised a method in which dimethyldioxirane was produced in the reaction medium. In this way, as a general procedure, to a mixture of the substrate (1 mmol), acetone (10 ml), water (10 ml) and Na_2CO_3 (1 g), Oxone (3 g) was added in portions until disappearance of the starting material was observed. Acetone was removed under vacuum and the mixture extracted with diethyl ether. After evaporation of the solvent, pure heterocyclic products **3** were obtained. Chromatographic purifications were performed only if required.

Table 1

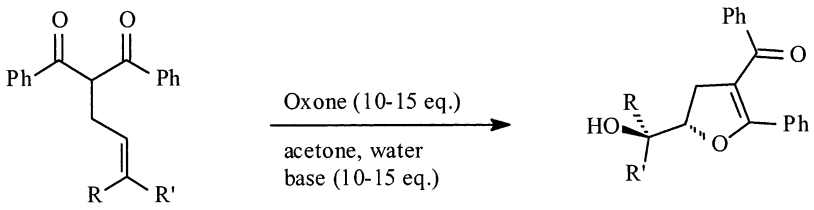


1 (a-d) **2** (a-d) **3** (a-d)

Entry	Substrate	R	R′	Base[a] (equiv.)	Temp. (°C)	Time (h)	Yield (%)
1	**1a**	H	H	NaH (1)[b]	25	24	92
2	**1a**	H	H	Na_2CO_3 (2)[c]	25	72	>96
3	**1a**	H	H	Na_2CO_3 (2)[b]	70	18	>96
4	**1b**	H	Me	NaH (1)[b]	25	2	75
5	**1b**	H	Me	Na_2CO_3 (2)[c]	25	44	75
6	**1b**	H	Me	Na_2CO_3 (2)[b]	70	24	>96
7	**1c**	Me	Me	NaH (1)[b]	25	0.5	83
8	**1c**	Me	Me	Na_2CO_3 (2)[c]	25	48	57
9	**1c**	Me	Me	Na_2CO_3 (2)[b]	70	24	>96
10	**1d**	H	Ph	NaH (1)[b]	25	17	86
11	**1d**	H	Ph	Na_2CO_3 (2)[c]	25	22	35
12	**1d**	H	Ph	Na_2CO_3 (2)[b]	70	5	>96

[a] NaH was used in THF, Na_2CO_3 in acetone–water.
[b] Base added to a solution of the isolated epoxide.
[c] Base added to the mixture after the epoxidation reaction.

Table 2



1 (a-d) **3** (a-d)

Entry	Substrate	R	R′	Base	Temp. (°C)	Time (h)	Yield (%)
1	**1a**	H	H	$NaHCO_3$	25	72	69
2	**1a**	H	H	Na_2CO_3	70	18	75
3	**1a**	H	H	Na_2CO_3	25	20	95
4	**1b**	H	Me	$NaHCO_3$	25	28	50
5	**1b**	H	Me	Na_2CO_3	25	36	70
6	**1c**	Me	Me	$NaHCO_3$	25	24	62
7	**1c**	Me	Me	Na_2CO_3	70	36	96
8	**1d**	H	Ph	Na_2CO_3	25	22	57
9	**1d**	H	Ph	Na_2CO_3	70	48	90

Table 2 shows the results obtained with this procedure. Products were obtained in good to excellent yields, also in the case of α-cyclohexenyl-β-dibenzoylmethane low conversions were observed under all conditions.

The process is stereospecific since when a 70:30 *trans*/*cis* diastereomeric mixture of **1b** was used, the same ratio of *erythro*/*threo* isomers of the dihydrofuran **3b** was recovered. Moreover, pure *trans* **1b** (or **1d**) gave only one diastereoisomer, presumably the *erythro* form, by S_N2 attack of the nucleophile.[10]

For **1c**, good results were obtained also in the absence of acetone, possibly by using the keto groups of the substrate as dioxirane precursor. The epoxidation occurred efficiently and the resulting epoxide underwent nucleophilic attack to give the corresponding cyclisation product **3c**. For all other substrates the same procedure led either to no conversion **1a**, undesired products, or complex mixtures.

In perspective, with the introduction of a recent method for asymmetric epoxidation using chiral dioxiranes,[11] this method could be useful for the preparation of optically enriched dihydrofurans.

In conclusion we have shown that in a one-step procedure, 2-alkenyl-1,3-dicarbonyl compounds can be cyclised efficiently with high regio- and stereocontrol, in a method of general value for the synthesis of dihydrofuran derivatives. Work is in progress to determine the advantages and limits of this approach.

References

1. Antonioletti, R.; Magnanti, S.; Scettri, A. *Tetrahedron Lett*. **1994**, *35*, 2619.

2. Antonioletti, R.; Bonadies, F.; Scettri, A. *Tetrahedron Lett*. **1988**, *39*, 4987. Antonioletti, R.; Cecchini, C.; Ciani, B.; Magnanti, S. *Tetrahedron Lett*. **1995**, *36*, 9019.
3. Nakanishi, K. *Natural Products Chemistry*; Kodansha Ltd.; Academic: New York, 1974. Meyers, A. I. *Heterocycles in Organic Synthesis*; John Wiley & Sons: New York, 1974. Danheiser, R. L.; Stoner, E. J.; Kojama, H.; Yamashita, D. S.; Klade, C. A. *J. Am. Chem. Soc*. **1989**, *111*, 4407. Vernin, G. *The Chemistry of Heterocyclic Flavoring and Aroma Compounds*; Ellis Horwood: Chichester, 1982.
4. Lipshutz, B. H. *Chem. Rev*. **1986**, *86*, 795.
5. Harding, K. E.; Tiner, T. H. *Comprehensive Organic Synthesis*; Pergamon: Oxford, 1991; Vol. 4, p. 663. Cardillo, G.; Orena, M. *Tetrahedron Lett*. **1990**, *46*, 3321. Staninets, V. I.; Shilov, E. A. *Russ. Chem. Rev*. **1971**, *40*, 272. Barluenga, J.; Tomàs, M.; Suarez-Sobrino, A. *Synth. Lett*. **1990**, 673. Chenevert, R.; Pacè, J.; Plantè, R.; Beaucage, D. *Synthesis* **1982**, 75. Rychnovsky, S. D.; Bartlett, P. A. *J. Am. Chem. Soc*. **1981**, *103*, 3963. Kurth, M. J.; Beard, R. L.; Olmstead, M.; Macmillan, J. C. *J. Am. Chem. Soc*. **1989**, *111*, 3712.
6. Antonioletti, R.; D'Onofrio, F.; Rossi, B. *Synth. Commun*. **2000**, in press.
7. See for instance: Bovicelli, P.; Lupattelli, P.; Mincione, E.; Prencipe, T.; Curci, R. *J. Org. Chem*. **1992**, *57*, 2182. Bovicelli, P.; Lupattelli, P.; Mincione, E. *J. Org. Chem*. **1994**, *59*, 4304. Bovicelli, P.; Lupattelli, P.; Mincione, E. *Chim. Ind*. **1995**, *77*, 298. Ballini, R.; Papa, F.; Bovicelli, P. *Tetrahedron Lett*. **1996**, *37*, 3507.
8. Antonioletti, R.; Bonadies, F.; Orelli, L. R.; Scettri, A. *Gazz. Chim. It*. **1992**, *122*, 237.
9. Baldwin, J. E. *J. Chem. Soc., Chem. Commun*. **1976**, 734. Delongchamps, P. *Stereoelectronic Effects in Organic Chemistry*; Pergamon: Oxford, 1983.
10. In the acetyl derivative of **3d**, the coupling constant of the proton adjacent the ester (C*H*–OAc) is 4.4 Hz as for the same proton in **3b** (4.3 Hz) derived from a cinnamyl ester, and in agreement with that previously observed for cyclisation reactions promoted by iodine (Ref. 2).
11. Wang, Z.-X.; Miller, S. M.; Anderson, O. P.; Shi, Y. *J. Org. Chem*. **1999**, *64*, 6443.