A GENERAL METHOD FOR ALKYLATING BUTENOLIDES; REDUCTION OF PRODUCTS TO 3-, 2,3-, AND 3,4-SUBSTITUTED FURANS

S. W. Pelletier*, Z. Djarmati, I. V. Mićović and S. D. Lajsić
Natural Products Laboratory, Department of Chemistry
University of Georgia, Athens, Georgia 30602

A simple method for the alkylation of butenolides is investigated. The method involves addition of appropriate diazo compounds to butenolides, followed by thermal decomposition and affords 4-, 3,4-, and 4,5-substituted γ-crotonolactones in high yields. Reduction of those products with DIBALH, provides the substituted furans in good to excellent yields.

We wish to report the generality of a method for the synthesis of substituted butenolides (γ-crotonolactones) from inexpensive and readily available starting materials.[1] This procedure is simple, involves the addition of diazo compounds to butenolides, followed by thermal decomposition, and affords 4-, 3,4-, or 4,5-substituted γ-crotonolactones in very good yields. The sequence shown in Figures 1 and 2 illustrates this synthesis in the preparation of 3-, and 4-substituted γ-crotonolactones.

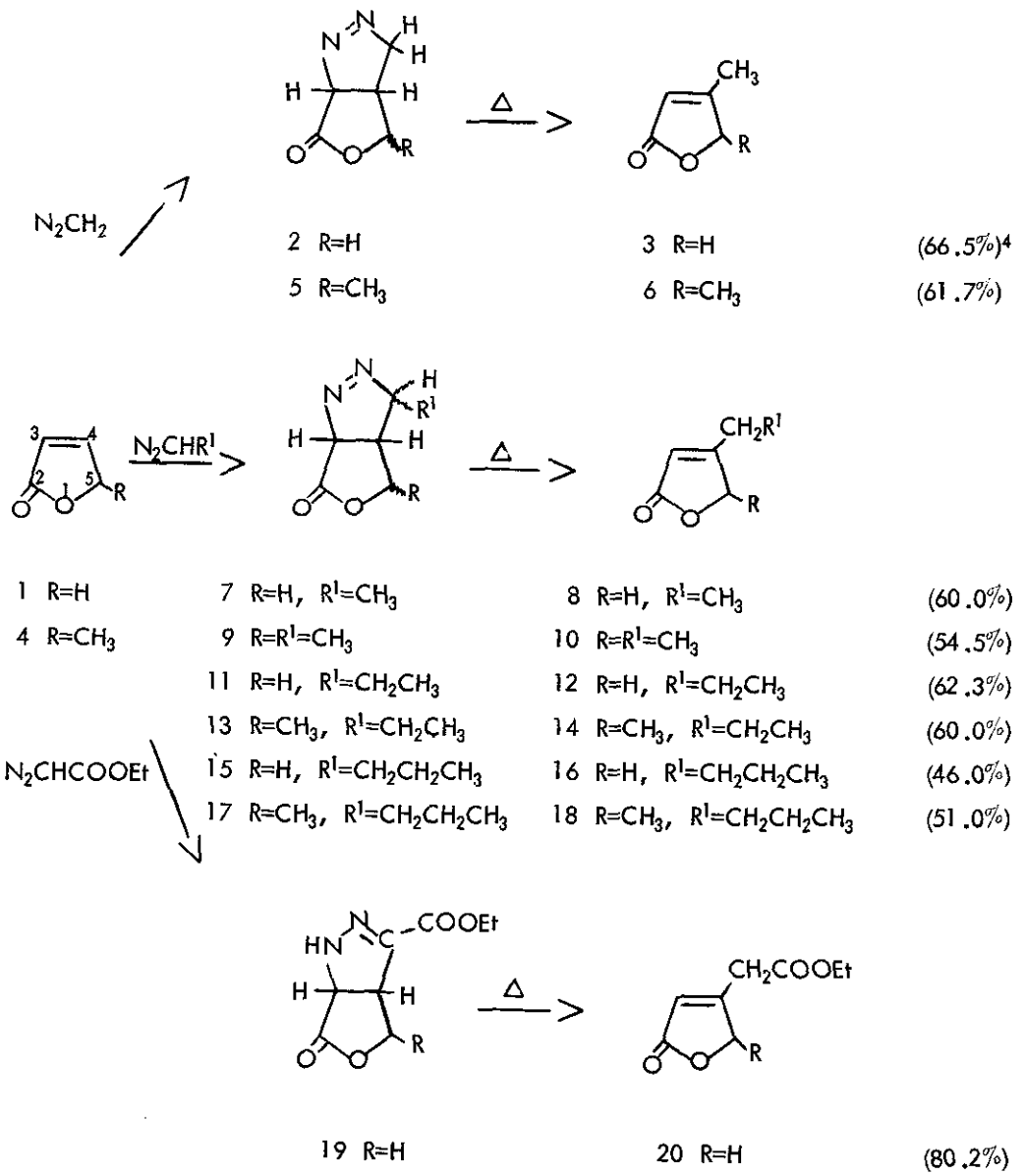
Because of the very limited availability of substituted butenolides, a simple method for their preparation is of considerable interest. This general method depends on the availability of a suitable diazo compound which can undergo 1,3-dipolar addition to a butenolide. The course of the synthesis depends on whether the butenolide is substituted in the 4 position. In the case when the 4 position is not occupied (Figure 1), the diazo compound adds to form a 1-pyrazoline (e.g. 2 or 7) or a 2-pyrazoline (e.g. 19)[2], which on thermal decomposition affords a 4-substituted butenolide (e.g. 3, 8, and 20). On the other hand, when position 4 is substituted (Figure 2), the addition of the diazo compound occurs in the opposite direction to form a 1-pyrazoline (e.g. 22 and 26)

which decomposes to yield a 3-substituted butenolide (e.g. 23 and 25). In our hands thermal decomposition of the pyrazoline-lactone adducts led in all cases to regeneration of the double bond and introduction of a side chain derived from the diazo compound. Specifically, compounds 3, 6, 8, 10, 12, 14, 16, 18, 20 (Figure 1) and 23, 25, 27, and 29 (Figure 2) have been synthesized. This procedure represents a direct method for introduction of a side chain on butenolides utilizing appropriate diazo compounds. The simplicity and the key details of the synthetic process are illustrated by the following two representative procedures for the preparation of compounds 3 and 20.

4-Methyl-2(5H)-Furanone (3). To a stirred solution of 18.0 g. of 2(5H)-furanone, 1, R=H, in 100 ml. of tetrahydrofuran at room temperature, an excess of ethereal diazomethane was added dropwise over a period of 15-20 minutes, and then stirred without heating for 8 hours. At the end of the reaction (as followed by t.l.c.) the crystalline pyrazoline-lactone adduct (2) was collected, yielding 18.5 g., m.p. 109-110°C. The solvent was removed under reduced pressure, leaving a residue of a colorless oil (5.5 g), which crystallized from ether to give 2.5 g., m.p. 107-109°, or a total yield of pyrazoline (2) from γ-crotonolactone (1) of 21.0 g (78%).

Compound 2 (5.0 g) was dissolved in 50 ml. of dioxane and heated in an oil bath with stirring for 48 hours at 120°. After removal of the solvent with a rotary evaporator, the yellow oil remaining was distilled to yield 3.0 g. (77.3%) of compound 3. Repeating the procedure using 15 g. of the pyrazoline-lactone adduct (2) gave 10.5 g. (90%) of (3), b.p. 112-113° at 14 mm/Hg. Compound (3) was established as 4-methyl-2(5H) furanone by comparison of i.r. and n.m.r. spectra with a sample prepared independently using the procedure of Fleck[3].

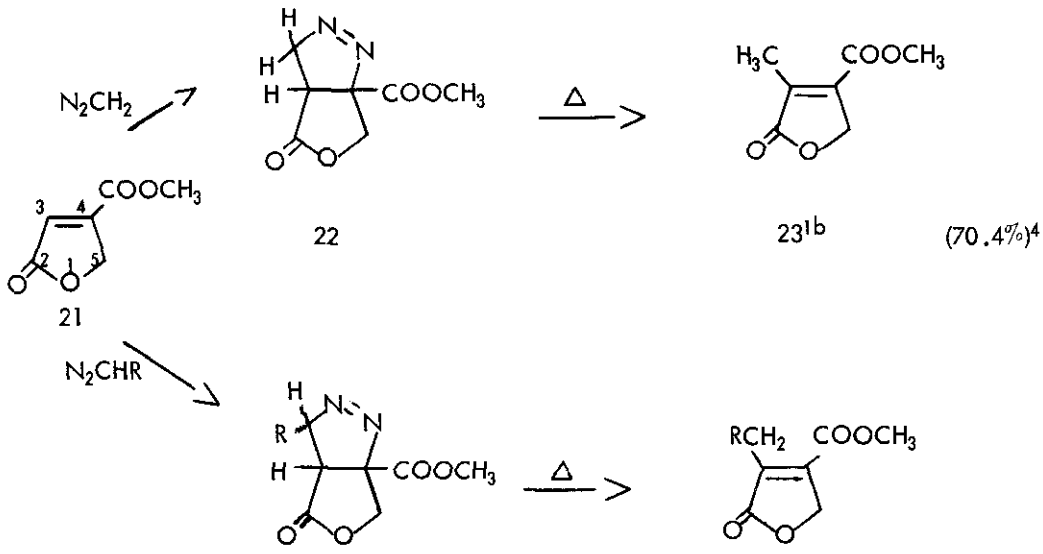
3-Hydroxymethyl-4-carboethoxy-but-2-enoic acid γ-lactone (20). To a stirred solution of 8.40 g of γ-crotonolactone in 50 ml. of dry dioxane was added at room temperature 13.00 g. (0.114 moles) of ethyl diazoacetate (analytical grade). The reaction mixture was refluxed for 12 hours in an oil bath. The excess of solvent was removed with a rotary evaporator and the crystalline material suspended in dry ether (50 ml.), collected, and washed with ether to remove any excess diazo compound. The yield of the crude product is essentially quantitative and after recrystallization from ether afforded 18.1 g. (92.5%) of 19, m.p. 136-137°C. Compound 19 (10.00 g.) was placed



	2 R=H	3 R=H	(66.5%)[4]
	5 R=CH_3	6 R=CH_3	(61.7%)
1 R=H	7 R=H, R^1=CH_3	8 R=H, R^1=CH_3	(60.0%)
4 R=CH_3	9 R=R^1=CH_3	10 R=R^1=CH_3	(54.5%)
	11 R=H, R^1=CH_2CH_3	12 R=H, R^1=CH_2CH_3	(62.3%)
	13 R=CH_3, R^1=CH_2CH_3	14 R=CH_3, R^1=CH_2CH_3	(60.0%)
	15 R=H, R^1=$CH_2CH_2CH_3$	16 R=H, R^1=$CH_2CH_2CH_3$	(46.0%)
	17 R=CH_3, R^1=$CH_2CH_2CH_3$	18 R=CH_3, R^1=$CH_2CH_2CH_3$	(51.0%)
	19 R=H	20 R=H	(80.2%)

Figure 1[5]

in 50 ml. of dry dioxane and heated in an oil bath with stirring for 48 hours at 150°C. After removal of solvent with a rotary evaporator, the yellow oil remaining was distilled to yield 7.45 g (86.8%) of compound 20, b.p. 148-150°C at 0.8 mm/Hg.



24 R=CH_3
25 R=CH_3 (67.4%)
26 R=CH_2CH_3
27 R=CH_2CH_3 (59.3%)
28 R=$CH_2CH_2CH_3$
29 R=$CH_2CH_2CH_3$ (52.6%)

Figure 2[6]

The synthetic sequence which is described herein should be useful for the synthesis of a variety of natural products possessing substituted butenolides as a side chain. The reaction conditions are so mild as to minimize the possibility of involvement of many functional groups. As is clear from the examples cited above the yields are remarkably high and there is very little variation in optimal conditions.

Recent reports[7] that α,β-unsaturated-γ-lactones attached to certain steroids or terpenes are reduced by diisobutylaluminum hydride (DIBALH) to the corresponding β-substituted furans, prompted to us to apply this reduction procedure to certain of the 3-, 3,4- and 4,5-substituted butenolides described above. In all cases, reduction

proceeded to furnish 3-, 2,3-, and 3,4-substituted furans in good to excellent yields (Figure 3). Thus the above described alkylation procedure, when coupled with reduction of the resulting alkylated butenolides, affords a convenient synthesis of difficulty accessible 3-, 2,3- and 3,4-substituted furans. The details of this work will be the subject of a subsequent publication.

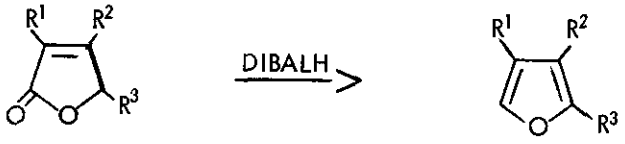


Figure 3

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REFERENCES

1a Franck-Neumann [Angew. Chem., International Edition in English, 1968, 7, 66] has reported that thermolysis in boiling benzene of the pyrazoline obtained by addition of 2-diazopropane to γ-crotonolactone, furnished 4-isopropylbutenolide. In the case of the corresponding pyrazoline from the 3-methyl-γ-crotonolactone thermolysis gave 80% of substituted butenolide and 20% cyclopropyl derivative. See also 1b. R. F. Rekker, J. P. Brombacher and W. Th. Nauta, Rec. Trav. Chim. Pays-Bas., 1954, 73, 417, and 1c. T. Uyehara, S. Hiyakoshi and Y. Kitahara, Syn. Commun., 1973, 3, 365. The generality of this reaction for the alkylation of butenolides has not been explored in any systematic manner. This paper demonstrates the generality and usefulness of this reaction sequence.

2 R. Huisgen and P. Eberhard, Tetrahedron Letters, 1971, 45, 4343-4346; 1971, 45, 4337-4342.

3 F. Fleck and H. Schinc, Helv. Chim. Acta, 1950, 33, 146.

4 The percentages indicate the overall yields from starting butenolide for the reaction

products after distillation. However, n.m.r. spectroscopic analysis of the crude, undistilled products showed no signs of the presence of any impurities, suggesting that the products are formed in essentially quantitative yield, and can be used without further purification. Because the reactions were carried out on a small scale losses during distillation were substantial. On a larger scale, the yields of the distilled products would undoubtedly be much higher.

5. All the products were identified by i.r., n.m.r., mass spectral analysis, and micro-analysis as well as by comparison with authentic samples where it was possible.

6. Thermolysis of the neat pyrazoline-lactone adducts should be carried out 20°C or less above melting point in order to prevent the rapid liberation of nitrogen. Thermolysis of the melt is not applicable on a large scale because sudden liberation of nitrogen may result in an explosion. This procedure is most useful for pyrolysis of 2-3 g. quantities of pyrazolines.

7. H. Minato, and T. Nagasaki, Chem. Commun., 1965, 377; H. Minato and Nagasaki, J. Chem. Soc., C. Org., 1966, 1866; H. Minato and T. Nagasaki, J. Chem. Soc., C. Org., 1968, 621.

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