# PREPARATION OF $^{18}O$-BILABELLED CARBOXYLIC ACIDS: CINNAMIC AND PHENYLPROPIOLIC ACIDS *via* STYRYLISOXAZOLES

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SUMMARY

3-Phenyl-2-propenoic (cinnamic) and 3-[$^{2}H_{5}$]-phenyl-2-propenoic $^{18}O$-bilabelled acids (2c,d) are prepared *via* alkaline hydrolysis of styrylisoxazoles (1a,b). The same reaction carried out on the *vic*-dibromocompounds (3a,b) gave the 3-phenyl-2-propynoic (phenylpropiolic) and 3-[$^{2}H_{5}$]-phenyl-2-propynoic $^{18}O$-bilabelled acids (4c,d), respectively.

KEY WORDS

Oxygen-18 and deuterium labelled compounds; 3-phenyl-2-propenoic and 3-phenyl-2-propynoic acids.

## INTRODUCTION

The importance of isoxazole derivatives as intermediates in organic synthesis is well established on the basis of the current literature on this topic (1-4). Moreover syntheses of natural

0362-4803/86/050487-07$05.00

Received November 28, 1985

products or related compounds, e.g. steroids (5) and (±)-[6]-gingerol (6) and corrins (7) were achieved by following strategies which involved isoxazole derivatives as a part of the synthetic routes.

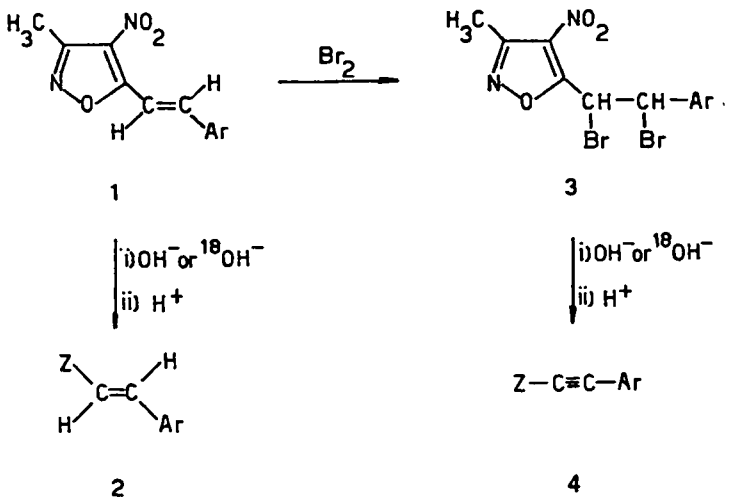
Under the former line we have already reported the preparation of cinnamic (8), coumaric (9) and phenylpropiolic (10) acids via styrylisoxazoles. The use of $Na^{18}OH$ ($^{18}O$ 20%) for the cleavage of the isoxazole ring in the preparation of cinnamic acid, allowed us to clarify the role of nucleophilic attack of the alkaline medium on the $C_5$ of the isoxazole ring which in turn became the carbon atom of the carboxylic group (11). In addition, $^{18}O$-bilabelled coumaric acid was also obtained by this route (9). Because the methods reported in the literature for the preparation of the $^{18}O$-bilabelled carboxylic acids mainly involve the use of $C^{18}O_2$(12), hydrolysis, or exchanging procedures with $H_2{}^{18}O$ (13), we found it interesting to extend our previous experiments to the preparation of cinnamic and phenylpropiolic acids with two $^{18}O$ in the carboxylic group.

## RESULTS AND DISCUSSION

The styrylisoxazoles (1a,b) used in this study as starting materials were obtained according to the literature (14) by condensing 3,5-dimethyl-4-nitroisoxazole with benzaldehyde and [$^2H_5$]-benzaldehyde respectively. Alkaline hydrolysis (NaOH 1N) of compounds 1a and 1b, followed by acidification, gave the expected cinnamic acids 2a (8) and 2b which showed peaks in the mass spectra at m/e=148, 147 and m/e=153, 152, respectively. These values were attributed to the corresponding molecular ions $M^+$ and $M^+-1$. When the same hydrolysis was carried out with $Na^{18}OH$ ($^{18}O$

99.8%), the mass spectra of the resulting acids showed signals at m/e=152, 151 and m/e=157,156. These findings were in agreement for $M^+$ and $M^+$-1 of the expected $^{18}O$-bilabelled cinnamic and 3-[$^2H_5$]-phenyl-2-propenoic acids 2c and 2d.

Alkaline hydrolysis (NaOH 1N) followed by acidification of 3a (10) and 3b gave the 3-phenyl- and 3-[$^2H_5$]- phenyl-2-propynoic acids 4a and 4b, which showed signals in the mass spectra at m/e=146 ($M^+$) and m/e=151 ($M^+$).




1 3

2 4

| Compound | Ar | Z |
|---|---|---|
| 1a, 3a | $C_6H_5$ | |
| 1b, 3b | $C_6D_5$ | |
| 2a, 4a | $C_6H_5$ | COOH |
| 2b, 4b | $C_6D_5$ | COOH |
| 2c, 4c | $C_6H_5$ | $C^{18}O^{18}OH$ |
| 2d, 4d | $C_6D_5$ | $C^{18}O^{18}OH$ |

Treatment of 3a and 3b with $Na^{18}OH$ ($^{18}O$ 99%) afforded 4c and 4d, whose peaks in the mass spectra appeared at m/e=150 ($M^+$) and m/e=155 ($M^+$). These values are consistent with those expected for

the molecular ion of $^{18}O$-bilabelled 3-phenyl- and 3-[$^{2}H_5$]-phenyl-2-propynoic acids 4c and 4d, respectively. It is noteworthy to consider that the above method, which implies only the use of $H_2{}^{18}O$ as labelling reagent, is based on the alkaline hydrolysis of the 3-methyl-4-nitroisoxazol-5-yl group,which is a masked carboxylic group.

This reaction appears to be candidate as a general method for preparing $^{18}O$-bilabelled carboxylic acids.

## EXPERIMENTAL

Mass spectral data of compounds 2a-d and 4a-b were taken by direct inlet in the LKB mass spectrometer, whereas a VG 70-70 EQ spectrometer was used for those of compounds 4c-d. $^{1}H$-N.M.R. spectra were recorded on a Perkin-Elmer R32 spectrometer and reported in p.p.m. with tetramethylsilane as internal standard. Elemental analyses were performed with a Perkin-Elmer 240C apparatus; percentage of deuterium in compounds 1b and 3b, was calculated for the right M.W. and found as hydrogen. 3-Methyl-4-nitro-5-styrylisoxazole (1a), cinnamic acid (2a), 5-(1,2-dibromo-2-phenylethyl)-3-methyl-4-nitroisoxazole (3a) and phenylpropiolic acid (4a) were prepared according to the ref. (14), (8), (15) and (10), respectively. Na$^{18}$OH was prepared by careful addition of Na to $H_2{}^{18}O$ (isotopic enrichment was 99.8% and 99% for the hydrolysis of 1a-b and 3a-b, respectively).

3-Methyl-4-nitro-5-(2-[$^{2}H_5$]-phenylethenyl)-isoxazole (1b)

Compound 1b was prepared by condensing 3,5-dimethyl-4-nitroisoxazole with [$^{2}H_5$]-benzaldehyde (Merck,98%) following the procedure reported in the literature (14) for 1a. Yield 80.6%, m.p. 154-155°C (from ethanol).

N.M.R. ($CDCl_3$): 2.57 (s, 3H, $CH_3$); 7.69 (AB system, 2H, $J_{AB}$= 16.6Hz).

Anal. Calcd. for $C_{12}D_5H_5N_2O_3$ : C, 61.26; H, 4.24; N, 11.95 Found: C, 61.39; H, 4.36; N, 12.15%.

3-[$^2H_5$]-Phenyl-2-propenoic acid (2b)

Compound 1b (g 0.350) treated as reported in ref. (9) for 2a gave 2b (g 0.148, 65% yield) which was purified by sublimation (110°C, 0.6 mmHg), m.p. 133°C.

$^{18}$O-Bilabelled 3-phenyl-2-propenoic acid (2c)

Compound 1a (g 0.030) treated with Na$^{18}$OH 1N (ml 0.5) as reported in ref. (9) for 2a , gave 2c, which was purified by sublimation (100°C, 0.6 mmHg).

$^{18}$O-Bilabelled 3-[$^2H_5$]-phenyl-2-propenoic acid (2d)

Compound 1b (g 0.013) treated with Na$^{18}$OH (ml 0.5), was heated (95°C) under stirring for 4 h. The cold mixture was then filtered and the solution acidified with hydrochloric acid (gas) to give the expected 2d which was purified by sublimation (g 0.001; 100°C, 0.6 mmHg).

5-(1,2-Dibromo-2-[$^2H_5$]-phenylethyl)-3-methyl-4-nitroisoxazole (3b)

Compound 3b was prepared by treating 1b (g 0.560) in $CS_2$ with bromine following ref.(11). Yield 71.8%, m.p. 168-169°C (from ethanol).

I.R.(KBr) : 1615, 1520, 1415, 1379, 1365, 1300, 1140 and 822 $cm^{-1}$

N.M.R. ($CDCl_3$) : 2.63 (s, 3H, $CH_3$); 5.55-6.45 (AB system, centered at 6.0, $J_{AB}$ = 12Hz).

Anal. Calcd. for $C_{12}D_5H_5N_2O_3Br_2$ : C, 36.47; H, 2.53; N, 7.09 Found : C, 36.76; H, 2.67; N, 7.11%.

3-[$^{2}H_5$]-Phenyl-2-propynoic acid (4b)

Compound 3b (g 0.400) was treated with NaOH 1N (ml 8) and heated (95°C) for 3 h. Unreacted 3b was filtered off (g 0.018) and the solution acidified with HCl (gas) to give the expected compound 4b (g 0.103) which was purified by sublimation (g 0.079; 55°C, 0.5 mmHg).

$^{18}$O-Bilabelled 3-phenyl-2-propynoic acid (4c)

Compound 3a (g 0.025) was treated with Na$^{18}$OH 1N (ml 0.5) and heated (95°C) for 4 h. The cold mixture was then filtered and the solution acidified with hydrochloric acid (gas) to give the expected compound 4c which was purified by sublimation (g 0.001; 107°C; 0.5 mmHg).

$^{18}$O-Bilabelled 3-[$^{2}H_5$]-phenyl-2-propynoic acid (4d)

Compound 3b (g 0.025) was treated with Na$^{18}$OH 1N (ml 0.5) and heated (95°C) for 4 h. The cold mixture was then filtered and the solution acidified with hydrochloric acid (gas) to give the expected compound 4d which was purified by sublimation (g 0.001; 90°C; 0.5 mmHg).

## ACKNOWLEDGMENTS

It is a pleasure to acknowledge support of this investigation by C.N.R., "Progetto Finalizzato Chimica Fine e Secondaria" during the years 1980-1983. We wish to thank Mr. S. Papaleo for the elemental analyses.

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