SOUTHERN BRAZILIAN JOURNAL OF CHEMISTRY
SOUTH. BRAZ. J. CHEM., Vol. 9 , N° 10, 2001

A VERSATILE PROCEDURE FOR THE SYNTHESIS OF NEW PRENYLATED CINNAMIC ACIDS

Irinel Badea[a], Philippe Cotelle[b] and Jean - Pierre Catteau[b]

[a]Department of Analytical Chemistry, Faculty of Chemistry, University of Bucharest, 2 - 14 Bv Regina Elisabeta 70346 Bucharest, ROMANIA ;
[b]Laboratoire de Chimie Organique Physique, Université de Lille I, 59650 Villeneuve d'Ascq FRANCE

ABSTRACT

The prenylated cinnamic acids can be obtained in excellent yields, in two steps, using first a one - step conversion of corresponding bromobenzaldehydes to corresponding prenylated benzaldehydes.

KEYWORDS: lipoxygenase inhibitors, metallation, n butyl lithium, prenylated cinnamic acid

RESUMO:

Os ácidos cinâmicos prenilados podem ser obtidos com rendimentos excelentes em duas etapas, a primeira sendo a conversão correspondente dos bromobenzaldeídos aos benzaldeídos prenilados. A segunda etapa envolve a reação de Perkin.

INTRODUCTION

Leukotrienes (LTs) are a family of important inflamatory mediators produced by an enzymic cascade which is initiated by the action of 5 - lipoxygenase (5 - LO) on arachidonic acid. Leukotrienes are significantly involved in immunoregulation and in a variety of diseases, including asthma, inflammation and various allergic conditions.

Our research group is interesed in the design, synthesis, isolation, conformations, dynamics and structure - biological activity relationships of this new class of inhibitors of arachidonate lipoxygenases. This paper reports our findings on the synthesis of new prenylated cinnamic acids. The inhibitory effect and the bio - analytical behaviour of 3 - [3,4 dimethoxy - 5 - (3-methylbut-2-enyl) phenyl] 2 propenoic acid have been tested in our laboratories.

DOI: 10.48141/SBJCHEM.v9.n10.2001.8_2001.pdf

Although a few selective inhibitors have been reported, most of them are difficult to be obtained[1,2]. Caffeic acid[3,4], which is one of the most common reagents, is a selective inhibitor for 5-LO and therefore of leukotriene biosynthesis. The phenolic natural products bearing isoprenoid substituents have been reported by many authors[5] to posses anti-inflamatory, antiallergic, antiviral and antitumor properties. This observation is important for us in future design strategy. The search for new synthetic approaches for the prenylated compounds is a continously growing area of investigation. Prenylated benzaldehydes are very rarely synthesized by the direct introduction of a prenyl group, the reason being that the methods used often give low yields, involve a multistep sequence and overoxidation problems[6,7,8].

An original and efficient procedure to obtain the prenylated benzaldehydes which are precursors in the synthesis of cinnamic acids is reported in this paper. To accomplish direct metallation of 3,4 dimethoxy benzaldehyde it was decided to look at the bromobenzaldehyde derivative, as an easily available substrate.

The 3,4 dimethoxy-(3-methylbut-2-enyl) benzaldehydes were synthesised using a modified procedure applied for the one-step convertion of bromobenzaldehyde to the corresponding hydroxybenzaldehydes[9]. Figure 1 shows the importance of achieving metallation in a direct manner.

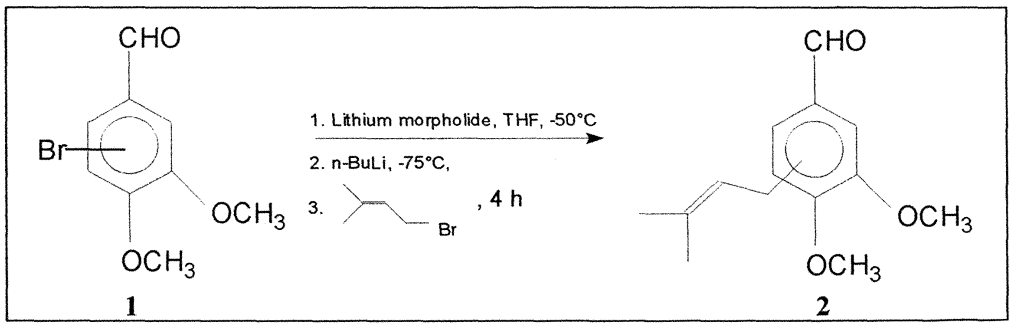

Figure 1. Conversion of bromobenzaldehyde to corresponding prenylated benzaldehyde

The method involves the in situ protection of the aldehyde function of the bromobenzaldehyde as its lithium morpholinoalkoxide, followed by lithium - bromide exchange and reaction with 1-bromo-3- methyl-but-2-enyl at -78°C. The usual procedure provided a crude mixture of 3,4 dimethoxy - (3-methylbut-2-enyl) benzaldehyde and 3,4 dimethoxybenzaldehyde which was purified by chromatography on silica gel with ethyl acetate : petroleum ether (3 : 2, v/v) as eluent, thus furnishing pure 3,4 dimethoxy-5-(3-methylbut-2-enyl) benzaldehyde in a 50 - 55% yield.

EXPERIMENTAL PROCEDURE

All chemicals used were analytical reagent grade. Packing material for column chromatography was Merck, silica gel 60 (70 - 230 mesh). Solvent used for metallation was thoroughly dried prior to use. Morpholine was stored over NaOH pellets under argon in a septum - capped bottle.

An oven - dried three - necked, round bottom flask equipped with a stirring bar, septum cap, thermometer and argon inlet was charged with morpholine (1 mL) and THF (20 - 30 mL). The mixture was cooled to - 50°C and a solution of n – butyl lithium in hexane was added all at once. After 10 minutes a solution of the bromobenzaldehyde (10 mmol) in 20 mL of THF was injected over a period of 5 min. and the mixture was allowed to cool to -70°C over 20 min. A solution of n – butyl lithium in hexane was then added dropwise, keeping the temperature at ~ -75°C. After 35 min a solution of 1-bromo-3-methylbut-2-enyl was added dropwise. Stirring was continued for an additional 4 h and the temperature was slowly increased to 0°C. The mixture was quenched with cold water, the solvent was removed in vacuo and the remaining aqueous phase was extracted twice with hexane. The basic aqueous solution was acidified with cold HCl and extracted with methylene chloride or ether. The extracts were washed successively with brine and water and dried over anhydrous sodium sulfate. Removal of the solvent yielded a crude material which was chromatographed.

Analytical characterization of the products gave the following results:

2a* : ***3,4 dimethoxy-2-(3-methylbut-2-enyl) benzaldehyde*** (12% from the NMR spectrum); **NMR ^{1}H** ($CDCl_3$) δ 1,68 (s, 3H, CH_3), 1,75 (s, 3H, CH_3), 3,70 (d, 2H Ph-CH_2=CH, J=7,20 Hz), 3,95 (s, 6H, 2xOCH_3), 5,16 (bt, 1H), 6,80 (d, $1H_{arom}$, J=9 Hz), 7,40 (d, $1H_{arom}$, J=9 Hz) 10,00 (s, 1H-CHO).*This compound can be obtained with a better yield using the procedure described by Crombie[7].

2b : ***3,4 dimethoxy-5-(3-methylbut-2-enyl) benzaldehyde*** (57%): pale yellow oil; **^{1}H NMR** ($CDCl_3$) δ 1,65 (s, 6H-2xCH_3), 3,30 (d, 2H Ph-CH_2=CH, J=7,34 Hz), 3,95 (s, 6H, 2xOCH_3), 5,16 (bt, 1H), 7,20 (s, $2H_{arom}$), 9,74 (s, 1H-CHO); **^{13}C NMR** ($CDCl_3$) 17,6 ppm (q, CH_3); 25,6 ppm (q, CH_3); 28,4 ppm (t, CH_2); 55,6 ppm (q, CH_3); 60,3 ppm (q, CH_3); 108,3 ppm (d, CH_{arom}); 121,9 ppm (d, CH); 125,9 ppm (d, CH_{arom}); 132,1 ppm (s, C); 133,0 ppm (s, C); 135,9 ppm (s, C); 152,6 ppm (s, C); 153,2 ppm (s, C); 191,3 ppm (d, CH); **IR** ($CHCl_3$) cm^{-1} 2900 - 2790, 1695, 1590, 1460;. **MS m/e** (percent, relative abundance) 234 (M^+, 40), 219 (M^+-CH_3, 27), 150 (100); Anal. Calcd for $C_{14}H_{18}O_3$ C, 71.76; H, 7.75 found C, 71.85; H,7.80.

2c : ***3,4 dimethoxy-6-(3-methylbut-2-enyl) benzaldehyde*** (48%) **^{1}H NMR** ($CDCl_3$) δ 1,70 (s, 6H-2xCH_3), 3,70 (d, 2H Ph-CH_2=CH, J=7,34 Hz), 3,95 (s, 6H, 2xOCH_3), 5,21 (bt, 1H), 6,70 (s, $1H_{arom}$), 7,35 (s, $1H_{arom}$), 10,17 (s, 1H-CHO); **^{13}C NMR** ($CDCl_3$) 18,0 ppm (q, CH_3); 25,6 ppm (q, CH_3); 30,4 ppm (t, CH_2); 55,9 ppm (q, OCH_3); 56,0 ppm (q, OCH_3); 110,6 ppm (d, CH); 112,4 ppm (d, CH); 123,1 ppm (d, CH); 126,6 ppm (s, C); 132,7 ppm (s, C) ; 140,0 ppm (s, C); 147,6 ppm (s, C); 153,8 ppm (s, C); 190,1 ppm (d, CHO); **IR** ($CHCl_3$) cm^{-1} 3000 - 2800, 1680, 1510, 1485;. **MS m/e** (percent, relative abundance) 234 (M^+, 40), 205 (M^+-CHO, 62); Anal. Calcd for $C_{14}H_{18}O_3$ C, 71.76; H, 7.75 found C, 71.70; H,7.60.

As the research was focused only on the synthesis of the 3 - [3,4 dimethoxy - 5 – (3-methylbut-2-enyl) phenyl] 2 propenoic acid (Figure 2), this compound was prepared using the general procedure of the Perkin reaction[10] changing only the time of reaction.

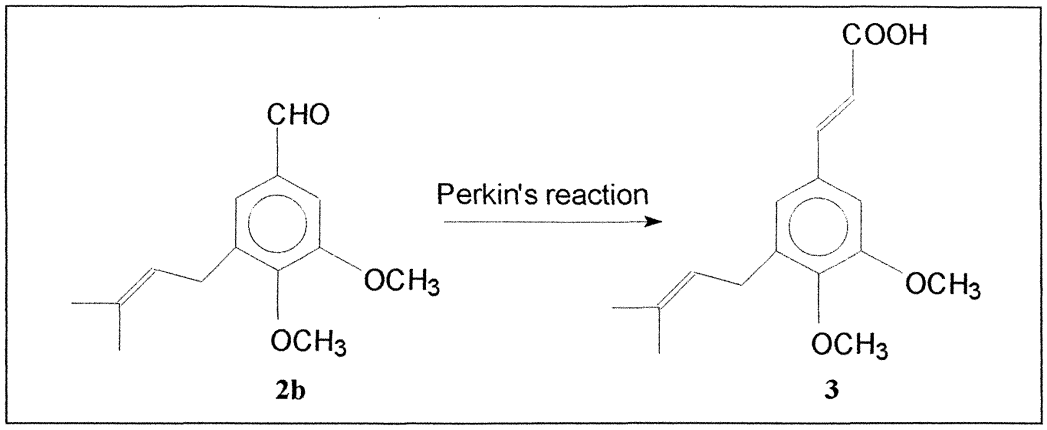

Figure 2. Synthesis of 3 - [3,4 dimethoxy - 5 - (3-methylbut-2-enyl) phenyl] 2 propenoic acid

3 - [3,4 dimethoxy - 5 - (3-methylbut-2-enyl) phenyl] 2 propenoic acid **^{1}H NMR** ($CDCl_3$) δ 1,75 (s, 6H-2xCH_3), 3,45 (d, 2H Ph-CH_2=CH, ^{3}J=7,34 Hz), 3,85 (s, 6H, 2xOCH_3), 5,25 (bt, 1H), 6,30 (dd 1H, ^{3}J=15,90 Hz), 6,90 (dd, 2H_{arom}, ^{4}J=1,93 Hz), 7,70 (dd, 1H, ^{3}J=15,90 Hz); **^{13}C NMR** ($CDCl_3$) 17,7 ppm (q, CH_3); 25,7 ppm (q, CH_3); 28,3ppm (t, CH_2); 55,6 ppm (q, OCH_3); 60,4 ppm (q, OCH_3); 109,1 ppm (d, CH_{arom}); 115,8 ppm (d, CH); 122,2 ppm (d, CH); 123,2 ppm (d, CH_{arom}); 129,6 ppm (s, C); 133,1 ppm (s, C); 136,1 ppm (s, C); 147,4 ppm (d, CH); 148,9 ppm (s, C); 152,9 ppm (s, C); 172,6 ppm (s, CH); **IR** ($CHCl_3$) cm^{-1} 3600 - 2400, 1700, 1630, 1410;. **MS m/e** (percent, relative abundance) 276 (M^+, 100), 206 (M^+-CH=CH-COO, 27), ; Anal. Calcd for $C_{16}H_{20}O_4$ C, 69.55; H, 7.30 found C, 69.55; H,7.36.

In a preliminary test the potency of these compounds as inhibitors of lipoxygenases was determined[11].

Summarising, a new and highly effective procedure for the synthesis of prenylated cinnamic acid is now available. Further work is in progress.

REFERENCES

1. R. M. Mc Millan, E. R. H.; Walker, *TiPS, 13*, 323 (1992).
2. J. H. Musser and A. F. Kreft, A.F. *J. Med. Chem., 35*, 2501(1992).
3. Y. Koshiara, T. Neichi, S. L. Murota, A. N. Lao, Y. Fujimoto ANDT. Tatsuno, *Biochim; Biophys. Acta., 792*, 92 (1984).
4. H. Cho, M. Ueda, M and M. Tamoaka *J. Med. Chem., 34*, 1503 (1994).
5. P. Manito, *Biosynthesis of Natural Products*, Ed. Ellis Horwood Limited London, England, 1981.
6. V. K. Ahluwalia and K.K. Arora, K.K., *Tetrahedron, 37*, 1437 (1981).
7. L. Crombie and S. V. Jamieson, *J. Chem. Soc. Perkin Trans. 1, 78*, 1467 (1982).
8. J. M. Saa, A. Llobera, A, G Raso, A. Costa and P. M. Deya, *J. Org. Chem., 53*, 4263 (1988).
9. R. T. Sinhababu and R.T. Borchardt, *J. Org. Chem., 48*, 1941 (1983).
10. R. J. Johnson, Ed., *Organic Reactions*, Adams, Wiley, (1942), - vol I, pp 210.
11. I. Badea, *Synthese et propriétés complexantes de nouveaux inhibiteurs potentiels des lipoxygenases*, Thesis, Université de Lille I, France, 1995.