Malonylation/Decarbalkoxylation of Furan Derivatives as Key Steps for the Preparation of Nonactic Acid Derivatives. Part II [1]

Jean-Mary Simone, François Loiseau, David Carcache, Pavel Bobal, Julie Jeanneret-Gris, and Reinhard Neier*

Institute of Chemistry, University of Neuchâtel, Neuchâtel, Switzerland

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Summary. A malonylation/decarbalkoxylation sequence from 2-substituted furans was investigated in view of developing a scalable synthesis of hydrophobic nonactic acid analogues.

Keywords. Heterocycles; Decarbalkoxylation; Nonactic acid; Natural-like.

Introduction
The ionophore nonactin is used in ion selective sensors because of its selectivity for ammonium and potassium cations [2]. The lifetime of these electrodes is limited due to the loss of nonactin through bleeding. In the course of our studies for the preparation of hydrophobic nonactin derivatives [3], we described a rapid synthesis of derivatives of nonactic acid from furan applying different radical couplings for the introduction of the first aliphatic side chain [4]. In Ref. [1], we described the introduction of the second aliphatic chain starting from malonyl derivatives as reagents. This transformation could be achieved in good yields and under total conversion of our starting materials. In this paper we present our results on the second decarbalkoxylation step (Scheme 1).

Results and Discussion
We first investigated the decarbalkoxylation of our dimethyl malonates 1–3. We studied the enzymatic mono-hydrolysis with pig liver esterase (PLE), followed by decarboxylation [5]. Applying PLE to this reaction is justified by the soft reaction conditions which are compatible with the heat-sensitivity of the furan derivatives. The selective enzymatic monomethylester hydrolysis for the two first products 1 and 2 occurred smoothly to give 4 and 5 in 63–64% yields (Scheme 2). To achieve complete hydrolysis of 2 proved to be more difficult; 24 h were required instead of the 4 h which were sufficient for the transformation of 1. The additional steric hindrance conferred to 2 by the introduction of the additional methyl group is probably responsible for the longer reaction times needed [6]. For 4 we measured the optical rotation, indicating that the enzyme is capable of distinguishing between the two enantiomeric ester groups. The enzyme was not able to hydrolyse the hydrophobic derivative 3. After heating 4 from 100 to 200°C at 0.019 Torr in the Kugelrohr in order to achieve the decarboxylation, only 43% of 6 were obtained. As the heat-sensitivity of furans is well documented this result did not come as a surprise (Scheme 2).

Since the enzymatic hydrolysis was not adequate for the transformation of the hydrophobic 3, we searched for alternative methods. Krapcho [7] and Van der Gen [8] use NaCl in wet DMSO. This reaction was successfully applied to 3 and gave 7 in 56% yield (Scheme 3). Total conversion of 3 was observed. The $R_f$ values on TLC of both 3 and 7 were almost the same. Separation
by column chromatography under the conditions studied would not have been possible. The heat sensitivity of furan derivatives can tentatively explain the loss of product once more.

To improve the yields we checked the consequence of reducing the reaction time. Under the conditions reported by Rapoport NaCl is replaced by LiCl [9]. Good yields could be obtained under these conditions heating for only 2 h at 190°C (Table 1). The first attempts using our model compounds 8 and 9 gave low yields of 25 and 23% of 17 and 18. To obtain these products two or four decarbethoxylations have to occur in sequence. The overall yield of such a transformation composed of several steps are by necessity relatively low even if the yield of the individual reaction is good to acceptable. We did not optimise these two transformations and focused our efforts on our target molecules 21–26. Transforming the free alcohol 10 under these conditions the yield of 19 was only 19%. We could isolate traces of the dimer 20 as side product. The formation of 20 can be explained as a transesterification of the ethylester part of one molecule of 20 with the alcohol part of a second molecule of 19. We assumed that other heavier oligomers and/or polymers were formed by poly-transesterification of 19, which could explain the low yield of isolated 19.

To avoid side reactions, we used the O-protected molecules 11–16. Under the same reaction conditions the O-benzylated molecules 11–15 gave 21–25 with satisfactory 63–91% yields. The O-acetyl protecting group of 16 was not resistant enough towards the reaction conditions. In this case, the yield in 26 was only 4%, and 14% of the deprotected product 19.