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Tetrahedron Letters 49 (2008) 3925–3926

Tetrahedron Letters

Tartradiamide formation by thermolysis of tartaric acid with alkylamines

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Received 5 March 2008; revised 26 March 2008; accepted 9 April 2008
Available online 12 April 2008

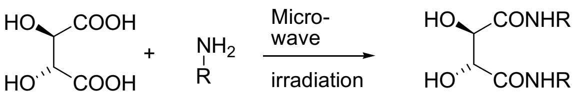
Abstract

The formation of *N*,*N*′-dialkyltartramides by microwave-assisted reactions and by conventional thermolysis was investigated. Thus, the thermolysis of L-tartaric acid with *n*-hexylamine at 200 °C showed that all the possible stereoisomers of *N*,*N*′-dihexyltartramide were formed albeit with partial racemization only. The same was observed for the microwave-assisted reaction.

Keywords: Thermolysis; Diastereoselective; Amphiphiles; Tartradiamide

The supramolecular properties of new optically active amphiphiles, in which tartaric diamides constitute the general base structures, are currently being studied by our group.[1] Synthesis of amides usually calls for multi-step reactions. Recently Plantier-Royon et al.[2] published a practical synthesis of a number of tartramides by microwave irradiation of L-tartaric acid in the presence of the appropriate amines at 180 °C, (Scheme 1).[2] Reported reaction times (12 min) were conveniently short and the yields were high. This was a variant of early syntheses of amides from carboxylic acids with amines.[3]

We therefore implemented this procedure for our purposes, and in our microwave equipment[4] comparable results were obtained. However, the supramolecular properties of products obtained from separate batches were not reproducible. Therefore the products formed, and the details of the reported microwave-assisted reaction were reinvestigated.



Scheme 1. Tartaric diamides via direct reaction of L-tartaric acid with amines.[2]

As a representative example, microwave irradiation[4] of (*R*,*R*)-tartaric acid, (*R*,*R*-**1**), with *n*-hexylamine for 45 min, starting at ambient temperature, gave **2** in 57% isolated yield, compared to the reported 81% yield.[2] However, as microwave irradiation functions by creating superheated conditions, we instead chose to perform the reaction using conventional thermolysis in a sealed tube at 200 °C, rather than at 180 °C as described for the microwave reaction. Thus, (*R*,*R*-**1**), was thermolyzed with 100% excess of *n*-hexylamine for 15 min, producing **2** in 68% isolated yield. NMR spectra of both crude products showed essentially complete conversion of (*R*,*R*-**1**).

The spectroscopic properties of the products obtained from both of these methods were similar to those reported for the Plantier-Royon microwave product.[2] The reported NMR spectra (proton and carbon), however, exhibited a number of signals that could not be accounted for. It was noted, that the reported elemental analyses as well as MS data were in full agreement with the proposed structures. Thus, what appeared to be a pure product may actually be a mixture of compounds. For our application of tartramides as structural entities in amphiphiles, full control of

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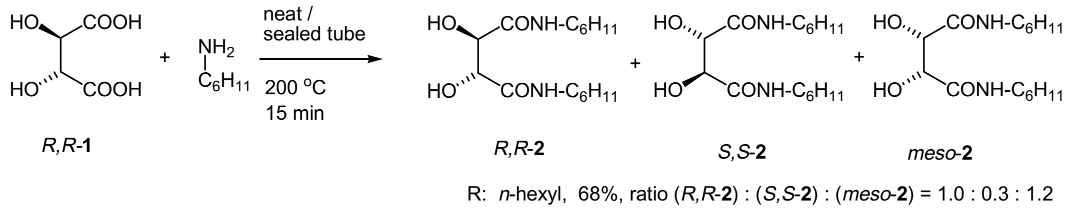
doi:10.1016/j.tetlet.2008.04.052



Scheme 2.

enantiomeric and chemical purity was of principal importance.

The proton NMR spectrum of product **2** in $CDCl_3$with the expected structure *R*,*R*-**2** exhibited two sets of signals. One set of signals was observed at 3.25 ppm (–CH_2–NH–), 4.23 ppm (d, $J = 7.5$ Hz) (HO–CH–), 5.48 ppm (d, $J = 7.5$ Hz) (–O H) and 7.07 (–N H–) ppm which constituted the main product, which was assigned the structure *R*,*R*-**2** or *S*,*S*-**2**.

A minor product exhibited characteristic signals at 3.30 ppm (–CH_2–NH–), 4.00 ppm (br s, HO–C*H*–), 5.69 ppm (br s, –O*H*) and 7.07 ppm (–N*H*–) ppm. In DMSO the –N*H*– signals were observed at 7.58 ppm as a triplet with $J = 6.0$ Hz for the major and at 7.45 ppm as a triplet with $J = 6.0$ Hz for the minor product. That the two sets of signals correlated were indicated by comparing the integrations of the NMR signals. HH-COSY experiments further confirmed this assignment.

The same two sets of signals were also observed for samples purified by multiple recrystallizations from acetonitrile, yielding products that appeared to be pure based on their elemental analyses and mass spectrometric characteristics. The variations in compositions of the crystallized products, as indicated, for example, by the NMR signals at δ 4.23 and 4.00 ppm, respectively, were accompanied with a fluctuation of melting points, indicating mixtures of products. Upon crystallization from toluene–acetonitrile (1:1) pure main product was isolated. The minor product was also obtained by recrystallization of the product isolated from the mother liquor, and was fully characterized. We reasoned the minor product to be *meso*-*N*,*N*′-dihexyltartramide (*meso*-**2**), based on its characteristic NMR data, and because isomerization was expected under the forcing reaction conditions. The structural assignment was further supported by the comparison of its spectroscopic data with those of an authentic sample.

The optical rotation of the worked-up, crude product **2** was$[\alpha]_D^{20}$ +28 (*c* 1.001, MeOH), which was comparable to the literature value of $[\alpha]_D^{20}$ +26.5 (*c* 0.4, MeOH).[2] This together with the NMR results clearly indicated that partial, though not complete, racemization had taken place during the course of the reaction. The ee value was approximately 28%. Authentic, pure *R*,*R*-**2** exhibited an optical rotation of $[\alpha]_D^{20}$ +93.5 (*c* 1.006, MeOH).

That more than one product was formed, but resulting in partial racemization only, was further confirmed by chiral column HPLC analyses of crude *N*,*N*′-dihexyltartramide, **2**, obtained either by conventional thermolysis or by microwave-assisted reaction of *R*,*R*-**2** with *n*-hexylamine. HPLC showed that the two enantiomeric diamides *R*,*R*-**2** and *S*,*S*-**2** appeared together with the *meso*-diamide, (*meso*-**2**), in a 1.0:0.3:1.2 ratio, (Scheme 2). Authentic diamides were acquired by reacting the appropriate dimethyl tartrate isomer with hexylamine in methanol at 5 °C.[5]

It was thus concluded that tartradiamide formation from tartaric acid and *n*-hexylamine readily took place either by conventional thermolysis or under microwave-assisted conditions. Extensive isomerization was established, though resulting in only partial racemization. The products were mixtures of all the possible dialkyltartradiamide stereoisomers. As a method for stereoselective synthesis of optically pure *N*,*N*′-dialkyltartramides, these procedures are of little practical value.

Acknowledgement

The authors wish to express their gratitude to the Department of Chemistry, Norwegian University of Science and Technology, NTNU for financial support.

Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2008.04.052.

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4. As we have to rely on a modified domestic microwave oven, experimental details are not revealed here.
5. U.S. Pat. 6,399,543, 2002; Chem. Abstr. **2002**, *137, 7814.*