From pregabalin to rac-3-cyano-5-methylhexanoic acid: an easy conversion which valorizes waste pregabalin enantiomer

Michael Zagami, Matteo Binda, Oreste Piccolò, Valentina Straniero, Ermanno Valoti, Marco Pallavicini

Dipartimento di Scienze Farmaceutiche, Università degli Studi di Milano, via Mangiagalli 25, I-20133 Milano, Italy
Studio di Consulenza Scientifica, via Bornò 5, I-23896 Sirtori (LC), Italy

A B S T R A C T

(S)-(+)-3-Aminomethyl-5-methylhexanoic acid (pregabalin) was converted in one-pot to (S)-(-)-3-cyano-5-methylhexanoic acid (pregabalin nitrile) by N-dichlorination and double dehydrochlorination. The (S) β-cyanoacid was racemized under mild conditions by treatment with a base. This very simple and efficient procedure, applied to (R)-(-)-3-aminomethyl-5-methylhexanoic acid, would enable the recycling of the undesired enantiomer of pregabalin, an anticonvulsant drug manufactured by the synthesis of rac-3-aminomethyl-5-methylhexanoic acid and subsequent classical resolution.

Pregabalin is (S)-(+)3-aminomethyl-5-methylhexanoic acid, a GABA (γ-aminobutyric acid) analogue developed for the treatment of epilepsy, neuropathic pain, anxiety and social phobia in the early nineties. More recent studies have shown its effectiveness of treating chronic pain in disorders such as fibromyalgia and spinal cord injury. Pharmacological properties reside in the S enantiomer of this γ-aminoacid. After its discovery as an anticonvulsant agent structurally related to gabapentin in 1993, thousands of scientific publications have appeared on pregabalin and, among them, some hundreds of process patents, most of which over the last few years. This increase in patenting activity is justified by the approach of the expiry date of the pregabalin patent, a drug whose world bulk production is about 200 tons/year. The resolution of racemic 3-aminomethyl-5-methylhexanoic acid, synthesized from diethyl malonate and isobutyaldehyde, with (S)-(+)-mandelic acid is one of the earliest patented pregabalin preparations, selected as a manufacturing process, after examining several different routes in considerable detail, on the basis of overall yield, cost and high process throughput.

Today, this route seems still cost-effective and its patent, among the industrially applied processes, is the nearest one to expiration date. Further improvements of the procedure are highly desirable and can be achieved by two ways; either by using an early as opposed to a late-stage resolution or by recycling the undesired enantiomer. We focused on the latter issue and we report herein a very easy and efficient procedure to recycle the off-isomer, namely (R)-(-)-3-aminomethyl-5-methylhexanoic acid.

Recently, we have studied the N-chlorination of different substrates such as aminoesters, aminodiesters, aminoimides and amides by dichloro- or trichloroisocyanuric acid. In particular,
we have efficiently racemized the undesired enantiomer of the N-benzylimide of cis-piperidine-2,3-dicarboxylic acid, a key intermediate of the antibiotic moxifloxacin, by (a) chlorination of piperidine nitrogen, (b) dehydrochlorination to give C(2)=C(3) double bond conjugated to imide carbonyls and (c) cis-hydrogenation (Scheme 2).6

These observations prompted us to consider the potential of N-chlorination to racemize the γ-aminoacid pregabalin. In this case, it was unlikely that a C=C double bond involving the stereogenic C(3) of pregabalin would result from N-dehydrochlorination so as to allow racemization by successive hydrogenation. However, we considered that the primary amine function of pregabalin might be dichlorinated; subsequent double dehydrochlorination would convert the dichloroaminomethyl group into nitrile. This would make the hydrogen of the stereogenic methyne, now in α-position to CN, acidic and allow the nitrile to be easily racemized by treatment with a base. Subsequent hydrogenation of racemic 3-cyano-5-methylhexanoic acid should be facile, since it is reported as the penultimate step in the pregabalin synthesis preceding the resolution and providing racemic 3-aminomethyl-5-methylhexanoic acid in high yield.6

The racemization experiments were carried out on the commercially available enantiomer (S)-(+)-3-aminomethyl-5-methylhexanoic acid (pregabalin) (Scheme 3). Trichloroisocyanuric acid (TCCA) was chosen as a chlorinating agent. According to De Luca and Giacomelli,10 the reaction between primary amines and equimolar TCCA under mild conditions gives the corresponding dichloroamines in very high or quantitative yields and not the nitriles as previously reported.11 Our experiments confirmed the N-dichlorination. Treatment of pregabalin with TCCA in dichloromethane at room temperature afforded the corresponding dichloroamine, which was isolated as an oil in near quantitative yield by simple filtration and concentration of the reaction mixture. The TLC analysis showed the disappearance of the starting substrate and the formation of a unique UV detectable product, eluted by relatively apolar mobile phases, such as cyclohexane/ethyl acetate mixtures, unable to carry up pregabalin.13 H NMR and elemental analyses were consistent with the formation of N-dichlorinated pregabalin as a single product and the mass spectrum showed the presence of two main peaks, namely a 228.07 m/z peak, equivalent to protonated N-dichloro pregabalin, with M+2 and M+4 peaks, of two-third and one-ninth intense respectively, and a 160.15 m/z peak (base peak), equivalent to protonated pregabalin. After verifying that N-dichlorination was quantitative, pregabalin nitrile was synthesized in one-pot from pregabalin without isolating the dichlorinated intermediate. Treatment of pregabalin in dichloromethane first with TCCA and then, after filtration, with triethylamine afforded (S)-3-cyano-5-methylhexanoic acid in 85% yield by simple concentration of the reaction mixture previously washed with aqueous HCl.12 The specific rotation was in agreement with the values previously reported in the literature for pregabalin nitrile.13,14

To racemize pregabalin nitrile, we screened a series of bases (triethylamine, sodium methoxide, potassium tert-butoxide) and solvents (methanol, isopropanol, DMF, acetone) at different temperatures (Table 1). We observed racemization only using potassium tert-butoxide in DMSO or in isopropanol. In particular, we found that this base induced racemization, which was complete after a few minutes in DMSO at room temperature or after 4 h in isopropanol at 80 °C. Under these latter conditions, optically inactive 3-cyano-5-methylhexanoic acid was obtained from (S)-3-cyano-5-methylhexanoic acid in 87% yield.15 The overall yield of the procedure, calculated on pregabalin, was 74%.

In conclusion, the conversion of pregabalin into pregabalin nitrile, which has never previously been considered, can easily be achieved via N-dichlorination and double dehydrochlorination. The subsequent quantitative racemization of the stereocentre under basic conditions offers the chance to access rac-3-aminomethyl-5-methylhexanoic acid by nitrile hydrogenation. We believe that such a procedure, applied to the R enantiomer of pregabalin, improves the preparation of pregabalin based on the resolution of rac-3-aminomethyl-5-methylhexanoic acid allowing the undesired enantiomer to be recycled. The recently reported comparison16 of the classical resolution of 3-aminomethyl-5-methylhexanoic acid with the enzymatic resolution of 2-carboxyethyl-3-cyano-5-methylhexanoic acid ethyl ester17 has to be reformulated on account of the present racemization method, which might be further improved by replacing DCM with a more environmentally friendly solvent.

Acknowledgment

We thank the Italian Ministry of University and Research for financial support.

References and notes


12. (+)-3-Aminomethyl-5-methylhexanoic acid (pregabalin) (2 g, 12.56 mmol) and trichloroisocyanuric acid (4 g, 17.21 mmol) were added to dichloromethane (30 ml) and vigorously stirred for 1 h at 5–10 °C and then for 2 h at room temperature. After cooling to 5 °C, the reaction mixture was filtered and the filtrate combined with 8.5 mL of triethylamine under stirring at 20 °C. After 1 h, triethylamine was removed by washing with 10% aqueous HCl and the organic phase washed with brine three times and concentrated to give 1.65 g of (+)-3-cyano-5-methylhexanoic acid (85%) as an oil: δ<sub>1</sub>H NMR (400 MHz, CDCl<sub>3</sub>) δ 9.50 (br s, 1 H), 3.09–2.99 (m, 1 H), 2.77 (dd, J = 17.2, 7.7 Hz, 1 H), 2.61 (dd, J = 17.2, 6.6 Hz, 1 H), 1.92–1.80 (m, 1 H), 1.66 (ddd, J = 13.8, 10.7, 4.95 Hz, 1 H), 1.36 (ddd, J = 13.8, 9.35, 5.2 Hz, 1 H), 0.99–0.95 (2 d, J = 6.6 Hz, 6 H) (see Ref.18). Anal. Calcd for C<sub>8</sub>H<sub>13</sub>NO<sub>2</sub>: C, 61.91; H, 8.44; N, 9.02. Found: C, 61.72; H, 8.47; N, 8.99. Filtration without addition of triethylamine and concentration of the filtrate afforded crude 3-dichloroaminomethyl-5-methylhexanoic acid as an oil in quantitative yield: 1<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 3.68 (dd, J = 12.9, 5.2 Hz, 1 H), 3.59 (dd, J = 12.9, 8.0 Hz, 1 H), 2.52–2.32 (m, 3 H), 1.68 (m, 1 H), 1.35–1.18 (m, 2 H), 0.93 (pseudo t, J = 6.8 Hz, 6 H); MS (ESI) m/z calcd for C<sub>8</sub>H<sub>13</sub>Cl<sub>2</sub>NO<sub>2</sub> (MH<sup>+</sup>): 228.06, found 228.07.


15. A solution of (+)-3-cyano-5-methylhexanoic acid (630 mg, 4.06 mmol) in 2-propanol was added to potassium tert-butoxide (1.05 g), heated at 80 °C for 4 h and then concentrated. The resulting residue was dissolved in dichloromethane and 1 N HCl. The organic phase was separated, washed with brine three times and concentrated to give 550 mg of rac-3-cyano-5-methylhexanoic acid (87%) as an oil: δ<sub>1</sub>H NMR identical to the S enantiomer.


