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# Synthesis of an oxa-lipoic acid☆

D. Srinivasa Reddy,* P. Srinivas, D. Balasubrahmanyam and Javed Iqbal

*Discovery Research, Dr. Reddy's Laboratories Ltd., Bollaram Road, Miyapur, Hyderabad 500 049, AP, India*

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**Abstract**—The synthesis of an oxa-lipoic acid is reported here for the first time. We have achieved the synthesis of the title compound starting from commercially available acrolein using a Michael addition and Knoevenagel condensation as key reactions.


Lipoic acid (LA) **1**, a naturally occurring octanoic acid derivative, has a critical role in energy metabolism as an essential co-factor for mitochondrial α-keto-acid dehydrogenases.[1] Besides its enzymatic role, LA has been shown to act as a micronutrient with a range of antioxidant and pharmacological properties.[2] More importantly, LA has been used for the treatment of diabetic complications and a recent study showed that LA can be used as an anti-obesity drug.[3] Despite its very attractive biological properties, it suffers from poor bioavailability. One of the reasons for its metabolic instability is β-oxidation.[4] Previous studies on metabolism have shown that LA is subject to extensive β-oxidation and major metabolites like bisnorlipoic acid and tetranorlipoic acids were identified.[4c] Recently, 3-keto-lipoic acid, an intermediate resulting from β-oxidation was detected in human plasma after oral dosing in a healthy volunteer.[4d] To address this issue, the β-methylene unit can be replaced with a group such as $-CF_2$, *N*-alkyl, or an oxygen atom. We have designed the title compound in which we replaced the β-methylene group with an oxygen atom (Fig. 1). Although, there are several reports in the literature on the synthesis of **1** and its derivatives,[5,6] no reports on the synthesis of the oxa-lipoic acid **2** are documented. In this Letter, we disclose the first synthesis of oxa-lipoic acid **2** starting from commercially available acrolein and benzylmercaptan.

We designed the synthesis of oxa-lipoic acid **2** such that the dithiolane moiety was introduced at a later stage due to its sensitivity towards various reaction conditions; in particular, it is prone to oxidation. Our synthesis began with the reaction of acrolein **3** with benzylmercaptan to give the aldehyde **4**.[7] Two-carbon homologation of compound **4** was achieved by heating with malonic acid monoethyl ester in the presence of piperidine and pyridine mixture to furnish **5** in 62% yield.[7] Addition of another molecule of benzylmercaptan in a Michael fashion resulted in compound **6**.[7] The alcohol **7**, obtained by $LiAlH_4$ reduction of **6** was subjected to O-alkylation with *t*-butyl bromoacetate under phase-transfer catalysis to furnish the ether **8** in 81% isolated yield. Removal of the *t*-butyl group in **8** by stirring with TFA in DCM gave the corresponding acid **9** in quantitative yield. The synthesis of oxa-lipoic acid **2** was achieved by construction of the dithiolane ring using a known procedure.[6h,i] Reductive removal of the benzyl groups with sodium–ammonia followed by oxidation furnished the oxa-lipoic acid as a viscous material in 50% isolated

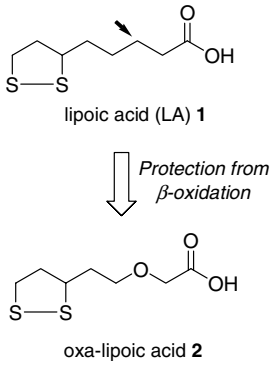


**Figure 1.** Protection from β-oxidation: replacement of β-methylene group with an oxygen atom.

*Keywords*: Lipoic acid; β-Oxidation; Metabolism.
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* Corresponding author. Tel.: +91 40 2304 5439; fax: +91 40 2304 5438; e-mail: dsreddy@drreddys.com

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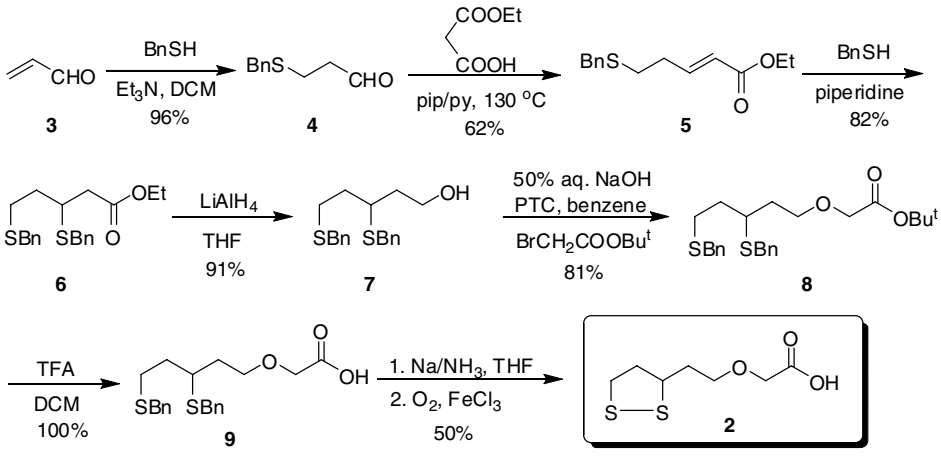


**Scheme 1.**

yield over two steps. The spectral data (IR, $^1$H NMR, $^{13}$C NMR and MS) of the **2** were in agreement with structure **2**[8] (see Scheme 1).

In conclusion, the first synthesis of oxa-lipoic acid **2** was achieved starting from acrolein and benzylmercaptan. Compound **2** was designed to resist from β-oxidation, which may help in improving the bioavailability of lipoic acid **1** by retaining its biological activity.

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8. Spectral data of **2**: IR (Neat): 1731 cm$^{-1}$; $^1$H NMR (400 MHz, DMSO-$d_6$): $\delta$ 12.54 (s, 1H), 3.99 (s, 2H), 3.77–3.71 (m, 1H), 3.54 (t, 2H, $J = 6.4$ Hz), 3.2–3.09 (m, 2H), 2.47–2.39 (m, 1H), 1.99–1.88 (m, 2H), 1.82–1.74 (m, 1H); $^{13}$C NMR (100 MHz, DMSO): $\delta$ 171.6, 69.4, 67.4, 52.8, 40.7, 39.8, 38.2; MS (CI): 208 (M$^+$).