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# Synthesis of anacardic acids by nucleophilic substitution on 2-aryloxazolines

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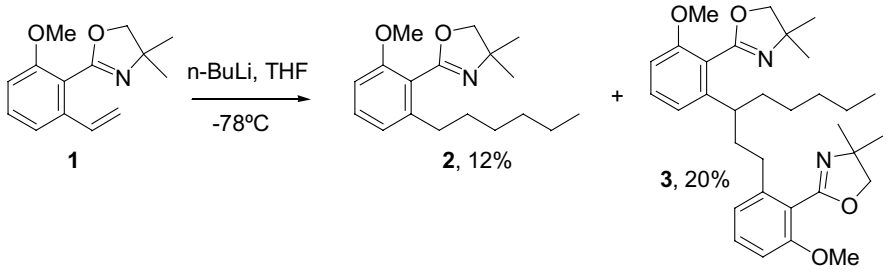
**Abstract**—A new direct synthesis for anacardic acids based in a nucleophilic substitution of a methoxy group in 2-aryloxazolines by long-chained Grignard reagents is reported.


Anacardic acids are natural products isolated mainly from cashew-nut shell (*Anacardium occidentale*). Essentially they are salicylic acid derivatives bearing a $C_{15}$ alkyl, alkenyl or alkatrienyl group in the 6-position.[1] Some other examples are the $C_{14}$, ginkgolinic acid[2] isolated from *Ginkgo biloba* or $C_{11}$, anagigatic acid[3] isolated from the pericarp of *Anacardium giganteum* and from *Schistochila appendiculata*. They are not exclusive of superior plants, but are also present in fungi as *Phlebia radiata* and *Hapalopilus mutans*[4] and marine organisms as *Pseudomonas* sp.[5] or *Haliclona* sp.[6]

These compounds are of interest because of their wide biological properties: antimicrobial,[7] antitumoural,[8] molluscicide,[9] antifungal,[10] insecticide,[11] regulation of gene expression,[12] etc. and have applications as antibacterial detergents, cosmetics, etc.[13] Therefore, several synthetic methods for anacardic acids have been reported.[14]

Previous studies[15] on the carbolithiation chemistry of styrene derivatives (where the 1,6-conjugated addition to *o*-vinylphenyloxazolines of alkyl and phenyllithium compounds occurs in good yields), suggest that this methodology can be a good alternative to the synthesis of anacardic acids, by starting from 2-methoxy-6-vinylphenyloxazoline **1**. However, it was observed that 2-vinylphenyloxazoline with a methoxy substituent in position-6, had a lack of reactivity when the reaction was carried out in diethyl ether.

An enhancement of the reactivity could be achieved by changing the solvent (i.e., THF), but the addition of *n*-BuLi to oxazoline **1** gave a low yield of a mixture of **2**, the expected addition product, and **3**, resulting from the addition of the benzylic anion on a molecule of starting material (Scheme 1). Other different attempts were checked to improve the reaction: solvents (THF, ether and hexane), temperatures (−55, −78 °C), reaction times




**Scheme 1.**

*Keywords*: Anacardic acid; Grignard reagent; Oxazoline.
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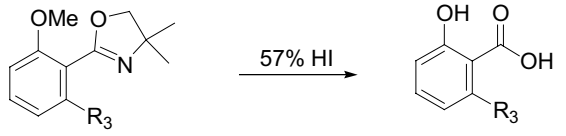
(5–120 min), even at high dilution. However from alkyllithium reagents a mixture of compounds **2** and **3** was always obtained. These unsuccessful experiments can be understood as a consequence of the steric hindrance of both substituents in *ortho*-positions, avoiding the coplanarity of phenyl and oxazoline ring.

However, the use of an oxazoline-based strategy to anacardic acids by the enhancement of previously reported low reactivity[16] of 2,6-dimethoxyphenyloxazolines towards organometallics could be quite useful. Thus, the reactivity of **5a** and **5b**, obtained from **4a** and **4b**, respectively,[16] with Grignard reagents was compared. The Grignard reagent methyl magnesium bromide led, as expected, to the substituted product **6a** from **5a** (yield 78%). However, 2,6-dimethoxyphenyloxazoline **5b** did not react after 4 days at room temperature. To the contrary, instead of replacing one of its methoxy groups, when the reaction was heated at reflux, experienced demethylation yielding phenol **7** (72% yield). This easy cleavage of O–C bond of the methoxy group of a phenyloxazoline with two methoxy groups in *ortho* was according with previously reported results by Meyers.[16]

The behaviour of the reactivity of both oxazolines (**5a**–**b**) towards long carbon-chain Grignard reagents ($C_{14}H_{29}$ and $C_{11}H_{23}$) was studied, since it was observed that butyl magnesium bromide afforded the substitution product **8a**–**b** (Table 1, entries 3–4), although reaction of **5b** required higher temperature than **5a** and proceed in moderate yield. Thus, the oxazoline **5b** reacted with Grignard reagent $C_{14}H_{29}MgCl$ after refluxing for 24 h, giving **9b** in 88% yield. However, for **5a** it was not necessary to reflux and after 1 day at room temperature compound **9a** was obtained in 64% yield (Scheme 2, Table 1, entries 5–6). Similar results were obtained for $C_{11}H_{29}MgCl$ (Table 1, entries 7–8). Therefore, it may be concluded that it is possible to obtain the substitution product in good yields (Table 1, entries 5–8) in the case of long chain Grignard reagents, although, as with *n*-BuMgBr, oxazolines **5b** require higher temperatures than **5a**. Notice that in all cases the oxazoline ring resists the reaction conditions without any observable addition product to the C=N bond by the Grignard.

Finally, to prepare the anacardic acids **11** and **12** it is necessary to cleave the oxazoline ring and the methoxy group. This was done in one step by using 57% HI and heating at reflux during 12 h, affording the corresponding alkyl salicylic acids in 75% and 88% yield, respectively (Scheme 3).

To sum up, a successful and direct way to prepare anacardic acids via *o*-methoxyphenyloxazolines and the corresponding Grignard reagents to introduce the alkyl branch is reported. All reactions proceed in good overall yield (50% for **9b** from 2,6-dimethoxybenzoic acid), and are highly competitive with previously reported synthesis for anacardic acids.[17]



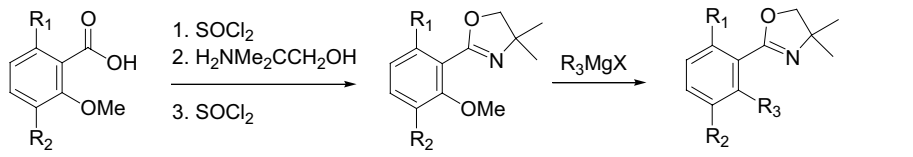

**9a**, **10a**

**11,** $R_3=C_{14}H_{29}$
**12**, $R_3=C_{11}H_{23}$

**Scheme 3.**

**Table 1.** Reactivity of 2-aryloxazolines with Grignard reagents

| Entry | Oxazoline | $R_3MgX$ | Temperature | Time (h) | Product | Yield (%) |
|---|---|---|---|---|---|---|
| 1 | **5a** | MeMgBr | Rt | 12 | **6a** | 78 |
| 2 | **5b** | MeMgBr | Reflux | 12 | **7** | 72 |
| 3 | **5a** | $C_4H_9MgBr$ | Rt | 17 | **8a** | 88 |
| 4 | **5b** | $C_4H_9MgBr$ | Reflux | 24 | **8b** | 49 |
| 5 | **5a** | $C_{14}H_{29}MgCl$ | Rt | 24 | **9a** | 64 |
| 6 | **5b** | $C_{14}H_{29}MgCl$ | Reflux | 24 | **9b** | 88 |
| 7 | **5a** | $C_{11}H_{23}MgCl$ | Rt | 24 | **10a** | 88 |
| 8 | **5b** | $C_{11}H_{23}MgCl$ | Reflux | 24 | **10b** | 71 |




**4a-b**

**a**: $R_1$= H, $R_2$= OMe
**b**: $R_1$= OMe, $R_2$= H

**5a-b**

**6a**, $R_3$= Me
**7**, $R_1$= OH, $R_2$= H, $R_3$= OMe
**8a-b**, $R_3$= $C_4H_9$
**9a-b**, $R_3$=$C_{14}H_{29}$
**10a-b**, $R_3$=$C_{11}H_{23}$

**Scheme 2.**

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