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A Convenient Preparation of Cyclobutyl Ketones: Naphthalene-Catalyzed Reductive Cyclization of Substituted 1,4-Dihalobutanes

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A Contribution from Synthesis Development; Pharmaceutical Process Development

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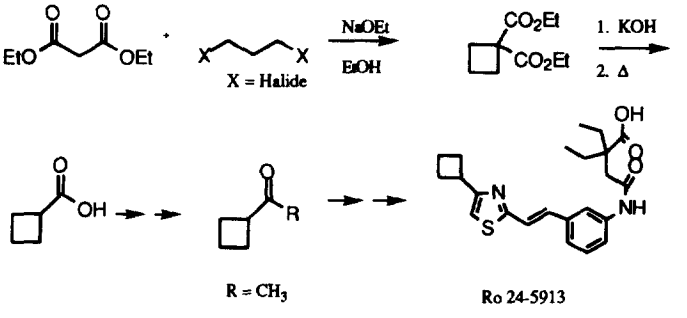
Abstract: *Acyl-substituted succinates are useful starting materials for the synthesis of cyclobutyl ketones. The key step, reductive cyclization of the intermediate dihalide, afforded yields of 32-60% of cyclobutyl-containing products.*

Cyclobutyl ketones have traditionally been prepared from the base-catalyzed reaction of 1,3-dihaloalkanes with substituted malonate esters. Saponification and decarboxylation of the resulting diester affords the key intermediate, cyclobutanecarboxylic acid. Standard functional group manipulation of the carboxylic acid moiety allows for entry into cyclobutyl ketones. (Scheme 1)[2]

Scheme 1



2 **1**

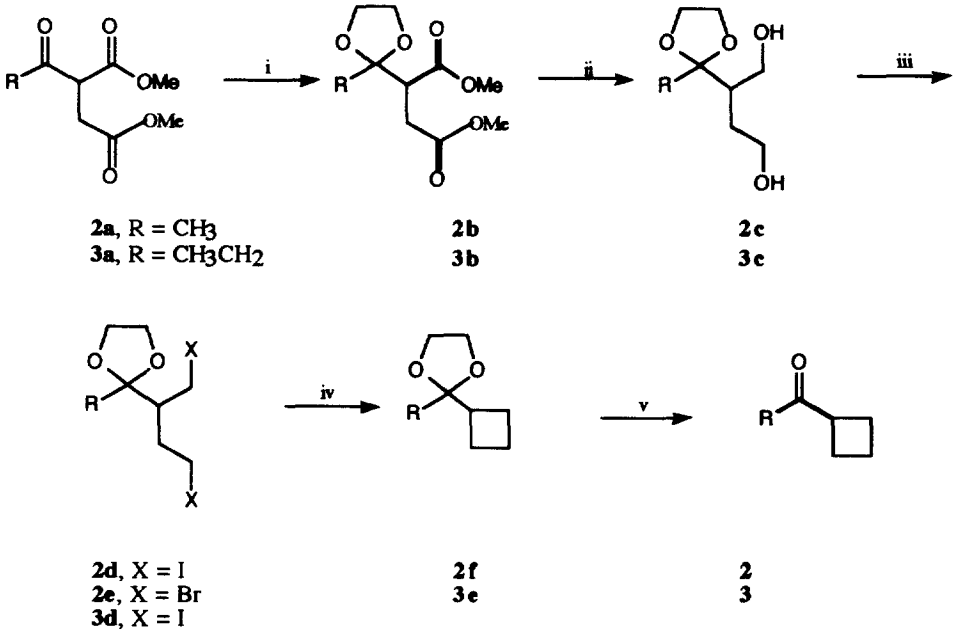
During the course of process research on the synthesis of leukotriene antagonist, Ro 24-5913 (**1**)[3], it became necessary to investigate alternatives to this present methodology for the preparation of cyclobutyl ketones and in particular, cyclobutyl methyl ketone (**2**). We wish to report on the results of that investigation.

The current technology for the preparation of cyclobutyl ketones (Scheme **1**) suffers from the fact that a carboxylic acid and not a ketone is the primary product of the synthesis. An additional step is necessary to convert the carboxylic acid group into the ketone. In addition, a wasteful activating group (i.e. a carboxyethoxy group) is required for the cyclization and the cyclization is essentially a two step process which requires first the attachment of the alkyl chain followed by ring closure. A more direct approach for the preparation of cyclobutyl

ketones would be highly desirable. To obviate these problems, an investigation of the utility of the readily available acyl-substituted succinates as starting materials for the preparation of cyclobutyl ketones was undertaken.[4] (Scheme 2).

The preparation of cyclobutyl methyl ketone **2** is used as an illustrative example. Dimethyl acetylsuccinate (**2a**) was treated with ethylene glycol and p-toluenesulfonic acid (p-TSA) in toluene to give ketal **2b**.[5] The ester groups were reduced with lithium aluminum hydride yielding diol **2c**.[6] Halogenation of diol **2c** with triphenylphosphine/halogen/imidazole gave dihalides **2d** and **2e**.[7] Treatment of diiodide **2d** with *t*-butyllithium in ether/pentane caused intramolecular reductive coupling to yield ketal **2f**.[8] Hydrolysis of ketal **2f** with aqueous hydrochloric acid yielded cyclobutyl methyl ketone (**2**).

Scheme 2



2a, R = CH_3 **2b** **2c**
3a, R = CH_3CH_2 **3b** **3c**

2d, X = I **2f** **2**
2e, X = Br **3e** **3**
3d, X = I

Reagents and Conditions: i. Ethylene glycol, p-TSA, toluene, reflux, 47%. ii. Lithium aluminum hydride, diethyl ether, reflux, 67%. iii. Halogen, triphenylphosphine, imidazole, dichloromethane 63-70%. iv. Lithium, cat.napthalene, THF, 0°C . v. Aqueous HCl, r.t. 45%, two steps.

Although we had demonstrated conceptually the correctness of our approach, the use of certain reagents and in particular the use of *t*-butyllithium necessitated the development of a less hazardous and costly alternative.

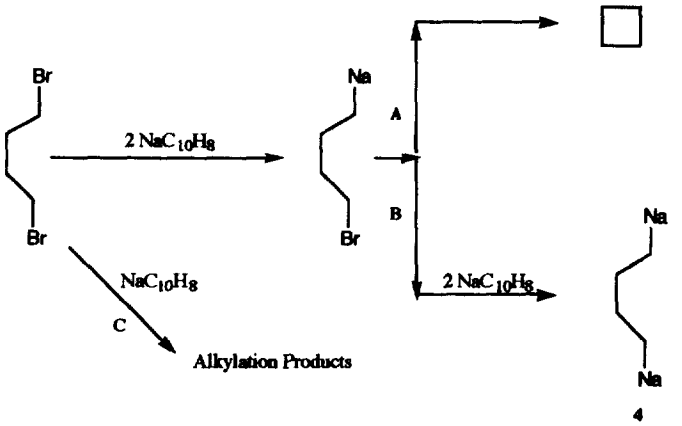
A review of the literature indicated only one potentially practical and high-yielding alternative. Previous workers were able to synthesize cyclobutane in a 70% yield by treatment of 1,4-dibromobutane with lithium/

mercury amalgam. Cyclobutane was also synthesized by the same group using a stoichometric amount of sodium naphthalenide, albeit in a 25% yield.[9a]

We rationalized that the low yield in the latter case was either the result of the formation of dianion **4** (Scheme 3) which cannot cyclize under the reaction conditions or due to alkylation of the napthalenide by starting material.[9b] Apparently, the intramolecular rate of cyclization (path **A**) is competitive with intermolecular rate of reduction by an additional radical anion (path **B**) or alkylation of the the starting material by the radical anion (Path **C**). Further, if this hypothesis is correct, then a low concentration of naphthalenide relative to dihalide should favor path **A** over paths **B** and **C**.

In the event, treatment of diiodide **2d** with an excess of lithium in the presence of 5 molar % of naphthalene resulted in the exclusive formation (TLC) of ketal **2f**. Subsequent deprotection with aqueous hydrochloric acid afforded a 45% isolated yield of cyclobutyl methyl ketone (**2**). In a similar fashion, the dibromide **2e** furnished a 32% yield of the cyclized ketal **2f** as the only isolable product.[10,11,12]

Scheme 3



In an analogous preparation, reaction of the higher molecular weight propyl homologue **3d** under comparable conditions afforded a 60% yield of the dioxolane **3e**. In a through process from the diiodide **3d**, a 67% yield of cyclobutyl propyl ketone (**3**) was obtained.[11]

In conclusion, an efficient synthesis of cyclobutyl ketones has been demonstrated. The salient feature of this approach is the use of a catalytic amount of napthalene in the critical reductive cyclization step.

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References and Endnotes

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10. The following is a representative example. Under a nitrogen atmosphere, naphthalene (42.4 mg, 0.331 mmol) was added to Li ribbon (919 mg, 132 mmol) in 30 mL of dry THF. The mixture was cooled to 0°C and a solution of dibromide **2e** (2.00 g, 6.62 mmol) in THF was added all at once. The mixture was stirred at room temperature overnight and was followed by an extractive workup with diethyl ether. After purification (radial chromatography, pentane, 5% diethyl ether/pentane), 301 mg (32%) of **2f** was obtained as a pale oil. Similarly, 77.3 mmol of diiodide **2d** was reacted as above and the crude reaction mixture was treated with 5% HCl at room temperature. An extractive workup was followed by an atmospheric distillation (BP = 135°C) to yield 3.0 g (45%) of cyclobutyl methyl ketone (**2**) as an oil.

11. All new compounds gave satisfactory spectral data and high resolution mass spectral data.

12. Despite the fact that ketal **2f** and ketone **2** were the only products observed by TLC, our crude and isolated material balances were low. This was attributed to the volatility of the products. In support of this hypothesis, the higher molecular weight propyl derivative afforded a significantly better yield of isolated products.

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