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A new facile method for the stereoselective synthesis of *trans*-2-aryl-3,3-dimethylcyclopropane-1-carboxylic acids

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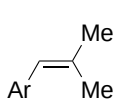
Abstract—A new facile method for the preparation of *trans*-2-aryl-3,3-dimethylcyclopropane-1-carboxylic acids was developed. The new method involved [2+2]-cycloaddition of styrenes with *N*,*N*,2-trimethylpropionamide followed by bromination and rearrangement of the resulting 3-aryl-2,2-dimethylcyclobutanones, affording the title compounds in two steps in 60–84% overall yields.

2-Aryl-3,3-dimethylcyclopropane-1-carboxylic acids are an important class of intermediates in organic synthesis. For example, they were used in the synthesis of biologically active compounds such as fungicides,[1] insecticides,[2–4] and acaricides.[3–5] More recently, 2-aryl-3,3-dimethylcyclopropane-1-carboxylic acids found applications in the synthesis of melatonergic agents,[6] and in the synthesis of sodium hydrogen exchanger inhibitors.[7]

Consequently, a number of methods have been developed for the synthesis of 2-aryl-3,3-dimethylcyclopropane-1-carboxylic acids. All these methods can be classified into four approaches according to the 2-aryl contributing starting materials. In the first approach, β,β-dimethylstyrenes **1** were used as the starting materials. While the reaction of **1** with diazoacetate affords the desired products, this approach is limited by the lack of stereoselectivity of the cycloaddition reaction, in addition to the hazards associated with diazoacetate.[8] In the second approach, α,α-dimethylacetophenones **2** were reacted with ethyl bromoacetate to give 3,3-dimethyl-4-aryl-γ-ketoesters which were subsequently transformed into the title compounds in four steps.[9] In the third approach, 2,2-dimethyl-3-arylbutan-2-ones **3** were used as the starting materials, which were obtained from benzyl halides and methyl isopropyl ketone.[10] Benzylic bromination of **3** followed by cyclobutanone ring formation and contraction gave the title compounds in three steps as a mixture of *trans*/*cis*-isomers.[10] In the fourth approach, cinnamates and derivatives **4** were used as the 2-aryl contributing starting materials to react with an isopropyl transfer reagent. While simple cinnamates **4** reacted successfully with diazoisopropane to give the desired products,[11] this reaction is also limited by its lack of stereoselectivity as well as by the difficulty in generating and handling the hazardous diazopropane.[11] A more user friendly isopropyl transfer reagent used in the cyclopropylation with **4** is *i*-propylidenetriphenylphosphorane.[12] This cyclopropylation reaction was highly stereoselective giving mainly the *trans*-products. The yields were, however, poor to moderate due to side reactions of the resulting products with *i*-propylidenetriphenylphosphorane.[12] While the side reactions associated with *i*-propylidenetriphenylphosphorane could be minimized by using *S*,*S*-diisopropyl-*N*-(*p*-tolylsulfonyl)sulfoximine,[13] application of the latter reagent is hampered by its availability. A more readily available and less expensive isopropyl transfer reagent is 2-nitropropane.[14] Activated cinnamate derivatives 4 (Y = CO_2R, SO_2R), however, were required for a successful cyclopropylation because of the reduced reactivity of the reagent. In addition, removal of the activating groups (Y = CO_2R, SO_2R) was problematic due to side reactions resulting from cyclopropane ring opening if a cyclopropane monocarboxylate product is desired.[7]



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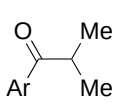

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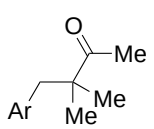

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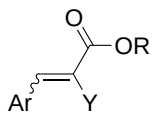

4

Y=H, CO_2R, SO_2R

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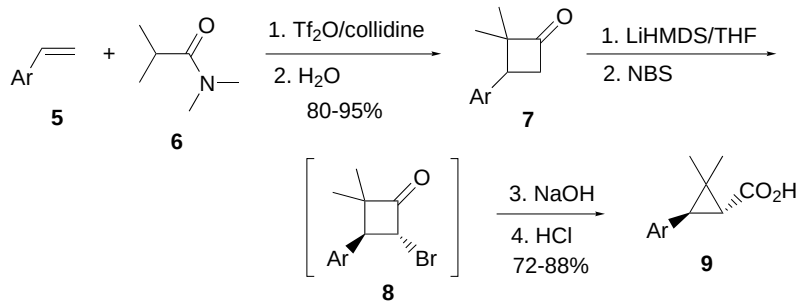

Scheme 1.

Table 1. Preparation of *trans*-2-aryl-3,3-dimethylcyclopropane-1-carboxylic acids **9**

Entry	Ar	Product	Yield%[a,b] (**7**)	Product	Yield%[a,b] (**9**)
1	4-$ClC_6H_4^-$	**7a**	93	**9a**	76
2	3-$ClC_6H_4^-$	**7b**	80	**9b**	81
3	3-$BrC_6H_4^-$	**7c**	86	**9c**	80
4	3-$MeOC_6H_4^-$	**7d**	80	**9d**	75
5	3-MeO-5-$ClC_6H_3^-$	**7e**	86	**9e**	72
6	2-F-5-$MeOC_6H_3^-$	**7f**	95	**9f**	88

[a] Isolated yield by chromatography or crystallization.
[b] All new compounds gave satisfactory spectroscopic and analytical data.

In our program of design and synthesis of novel arylcyclopropanecarboxyl guanidines as potent and selective sodium hydrogen exchanger inhibitors,[7] we required easy access to large amounts of various *trans*-2-aryl-3,3-dimethylcyclopropane-1-carboxylic acids **9**. While many of the desired compounds could be prepared using the first and fourth approaches described above, attempts to prepare other analogs using these approaches failed. Herein, we describe a new facile method for the stereoselective synthesis of *trans*-2-aryl-3,3-dimethylcyclopropane-1-carboxylic acids.[15] Our method begins with the readily available β,β-unsubstituted styrenes **5** as the 2-aryl contributing starting materials (Scheme 1).[15]

Thus, treatment of *N*,*N*,2-trimethylpropionamide **6** with 1.1 equivalents of trifluoromethane-sulfonic anhydride in methylene chloride at −15°C for 10 minutes followed by addition of 4-chlorostyrene **5a** and collidine and heating the reaction mixture at reflux for 4 hours afforded 3-(4-chlorophenyl)-2,2-dimethylcyclobutanone **7a** in 93% isolated yield after aqueous work-up.[16] Treatment of **7a** with 1.1 equivalents of LiHMDS in THF at −78°C followed by quenching the resulted enolate with one equivalent of *N*-bromo succinimide at the same temperature and warming the reaction mixture to 0°C for 20 minutes gave 2-bromo-3-(4-chlorophenyl)-4,4-dimethylcyclobutanone **8a** in solution. The product **8a** is expected to have the *trans*-configuration as bromination of the enolate generated from **7a** should take place from the opposite side of the 4-chlorophenyl ring due to a steric effect. Addition of aqueous sodium hydroxide to the in situ formed α-bromoketone **8a** resulted in a fast rearrangement reaction,[17,18] giving the desired product **9a** in one hour in 76% isolated yield after acidification and product crystallization. The reaction was highly stereoselective, affording *trans*-**9a** as a single isomer based on HPLC and ^{1}H NMR analyses. Importantly, the [2+2]-cycloaddition of styrenes **5** with **6** and subsequent bromination and rearrangement reactions appeared to be general for the preparation of a variety of 2-aryl-3,3-dimethylcyclopropane-1-carboxylic acids (Table 1). In all cases, the product was obtained as a single *trans*-isomer.

In summary, a new facile method for the stereoselective synthesis of *trans*-2-aryl-3,3-dimethylcyclopropane-1-carboxylic acids was developed. The new method involved [2+2]-cycloaddition of styrenes with *N*,*N*,2-trimethylpropionamide followed by bromination and rearrangement of the resulted 3-aryl-2,2-dimethylcyclobutanones, affording the title compounds in two steps in 60–84% overall yields. Compared to the previous methods developed for preparation of the title compounds, the new method not only uses more readily available starting materials and avoids the use of hazardous or difficult to obtain reagents, but is also manipulatively simpler and gives higher overall yields. More significantly, the new method is highly stereoselective, affording the *trans*-product as a single isomer. The application of *trans*-2-aryl-3,3-dimethylcyclopropane-1-carboxylic acids to the synthesis of other biologically active agents will be reported in due course.

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