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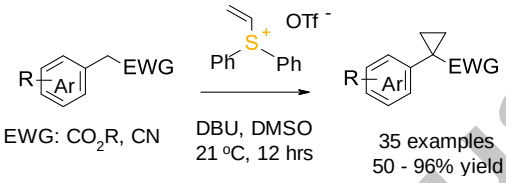

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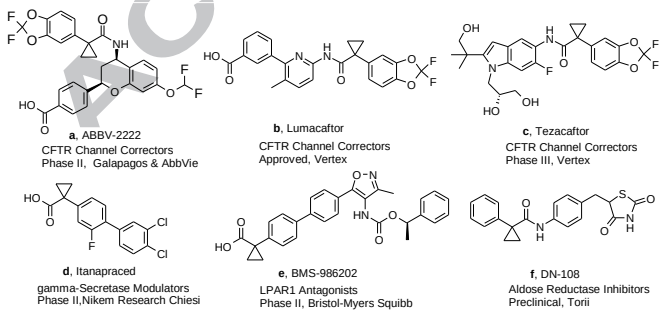
ABSTRACT

A convenient method was developed for the cyclopropanation of aryl acetates and aryl acetonitrile using vinyl diphenyl sulfonium triflate salt. The newly developed conditions are simple, mild, and compatible with a wide range of functional groups, without the need to apply an inert atmosphere, or alkali bases.

Introduction

Cyclopropyl-containing molecules are widely utilized in synthetic organic chemistry and highly useful in medicinal chemistry.[1] In medicinal chemistry, the introduction of a cyclopropyl moiety often enables the modification of molecular properties such as lipophilicity, aqueous solubility and conformation, as well as influences biological activity, metabolic stability and toxicity. As such, the cyclopropyl moiety is frequently present in preclinical candidates and clinical compounds.[2]



Scheme 1. Clinical compounds or preclinical candidates containing phenylcyclopropanecarboxylic acid or its derivatives.

The phenylcyclopropanecarboxylic acid motif is one of the key scaffolds in clinical or preclinical compounds for the prevention and treatment of cystic fibrosis and neurodegenerative diseases (Scheme 1).[3] To date, the most common synthetic route to phenylcyclopropanecarboxylic acid involves initial preparation of the corresponding acetonitrile precursors (Scheme 2).[3,4]

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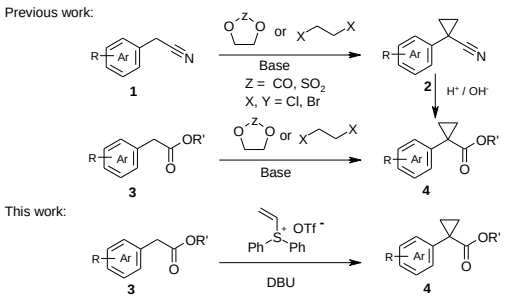
In general, the reaction is carried out using either dimethyl carbonate (DMC), ethylene sulfate or ethylene dihalogens as the alkylating agent in the presence of a strong base such as sodium hydride, sodium alkoxide, lithium hexamethyldisilazide (LHMDS) or aqueous sodium hydroxide, as well as a phase transfer catalyst (PTC). Despite moderate to good yields, the use of highly toxic NaCN and KCN in preparing the acetonitrile precursors, restricts the widespread application of this method. Another approach starts with the corresponding phenylacetate.[5] Similarly, the reaction utilizes DMC, ethylene sulfate and ethylene dihalogens as the alkylating agent in the presence of a strong base such as sodium hydride, sodium alkoxide, or LHMDS. However, the yields are often low.[5] In addition, the reaction can be sensitive to air and moisture due to the reactivity of the strong alkali base. Furthermore, the presence of a strong base will most likely deprotonate -OH and –NHR containing functional groups to generate the corresponding alkylation by-products.

Recently, we reported the highly efficient cyclopropanation of oxindoles with vinyl diphenyl sulfonium triflate.[6] Numerous advantages using the vinyl diphenyl sulfonium as the cyclopropanation reagent were disclosed, such as high yields, mild reaction conditions, good reaction selectivity, and the potential for broad application in late-stage functionalization. Additionally, vinyl sulfonium salts can be easily prepared using robust and safe protocols from 2-bromoethanol.[7] Herein, we report the application of this efficient cyclopropanation protocol to aryl acetates as well as aryl acetonitriles, which significantly broadens the scope of this cyclopropylation methodology.

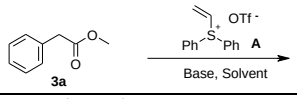


Scheme 2. Synthetic routes towards phenylcyclopropanecarboxylic acid derivatives.

Results and Discussion

Initially, the cyclopropanation of methyl 2-phenylacetate **3a** with vinyl diphenyl sulfonium salt was examined using CH_2Cl_2 as the reaction solvent. After screening a variety of bases, DBU was found to give the desired cyclopropylated product **4a** in 20% yield, which was more efficient than the reactions using triethyl amine (TEA), diisopropylethylamine (DIPEA), and cesium carbonate (Table 1, entry 3 vs. entries 1 and 2). Through solvent screening (Table 1, entries 3, 5-7) and adjustment of base equivalents (Table 1, entries 7 and 8), it was found that polar aprotic solvents such as DMF and DMSO were superior to CH_2Cl_2 and MeCN leading to higher yields, and that the yields were correlated to the solvent polarity. Specifically, the optimized reaction conditions were identified as those in entry 8 of Table 1. Conducting the reaction at a lower temperature (0 ^oC) or under an inert atmosphere did not significantly affect the reaction yield (Table 1, entries 9 and 10).

Table 1. Optimization of the reaction conditions.[a]

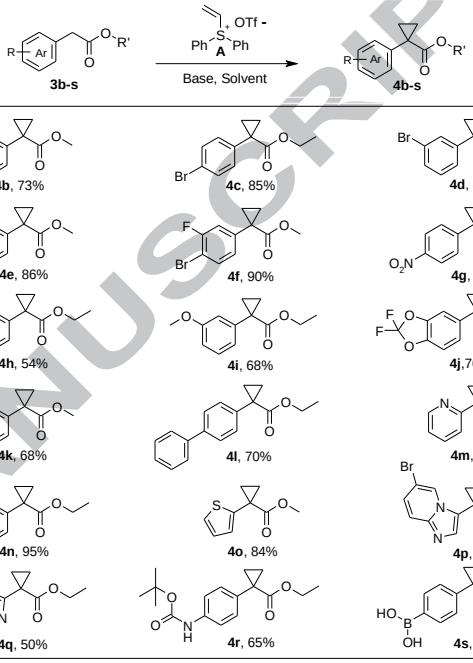


Entry	Base (equiv.)	Solvent	Yield **4a** (%)[d]
1	TEA (2.0)	CH_2Cl_2	0
2	DIPEA (2.0)	CH_2Cl_2	0
3	DBU (2.0)	CH_2Cl_2	20
4	Cs_2CO_3 (2.0)	CH_2Cl_2	0
5	DBU (2.0)	MeCN	46
6	DBU (2.0)	DMF	65
7	DBU (2.0)	DMSO	70
8	DBU (3.0)	DMSO	73
9[b]	DBU (3.0)	DMSO	74
10[c]	DBU (3.0)	DMSO	74

[a]Reagents and conditions unless otherwise specified: **3a** (0.2 mmol), **A** (0.24 mmol), base, solvent (1 mL), 21 ^oC, without a N_2 atmosphere, 12 h; [b]Reaction conducted at 0 ^oC; [c]Reaction conducted with a N_2 atmosphere; [d]Isolated yield.

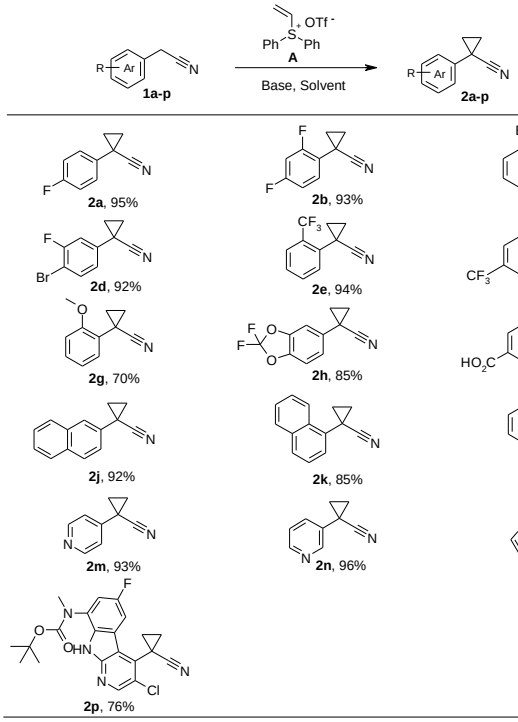
With the optimized conditions in hand, we then examined the scope of aryl acetate substrates for cyclopropanation. As shown in Table 2, substrates containing both electron donating groups (e.g. methyl, methoxy), and weak or strong electron withdrawing substituents (e.g. halogen, nitro), generated the corresponding cyclopropanation products in moderate to excellent yields (Table 2, **4b-j**). In particular, 1-(2,2-difluoro-1,3-benzodioxol-5-yl)cyclopropanecarboxylic acid ester (**4j**), as the key intermediate for the clinic candidates Lumacaftor, Tezacaftor, and ABBV-2222, was obtained with 76% yield (Table 2, **4j**). The literature preparations of such compounds proceed through complicated routes with lower yields for the cyclopropanation product.[8] In addition, heteroaryl acetates bearing a pyridine (Table 2, **4m, 4n**), thiophene (Table 2, **4o**), imidazo[1,2-a]pyridine (Table 2, **4p**), or thiazole (Table 2, **4q**) reacted smoothly to afford the corresponding cyclopropanation products. It should be noted that substrates containing functional groups such as NH_2, NHBoc, and boronic acid (Table 2, **4q**, **4r**, and **4s**, respectively) also led to the desired cyclopropyl containing products without *N*- or *O*-alkylation, demonstrating a wide range of functional group compatibility. However, this cyclopropanation reaction cannot take place for alkyl acetates due to the significant lower acidity of the alpha proton.

Table 2. Reaction scope and isolated yields for the cyclopropylation of aryl acetates.[a,b]



[a]Reagents and conditions: **3** (1 mmol), **A** (1.2 mmol), DBU (3 mmol), DMSO (5 mL), 21 ^oC, 12 h; [b]Isolated yield.

Table 3. Reaction scope and isolated yields for the cyclopropylation of aryl and heteroaryl acetonitriles.[a,b]

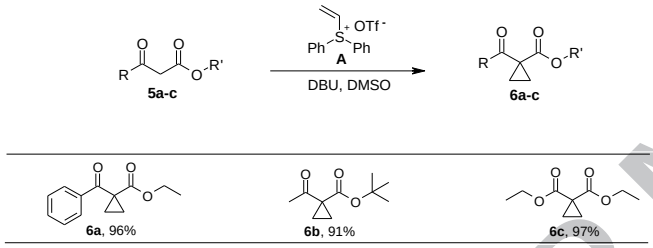


[a]Reagents and conditions: **3** (1 mmol), **A** (1.2 mmol), DBU (3 mmol), DMSO (5 mL), 21 °C, 12 h; [b]Isolated yield.

Subsequently aryl acetonitrile substrates were explored as shown in Table 3. The reactions proceeded smoothly for aryl substrates in which the aryl groups is substituted with either electron donating groups (e.g. methyl, methoxy), or electron withdrawing groups (e.g. trifluoromethyl, halogen), affording the corresponding cyclopropanation products in good to excellent yields (Table 3, **2a-l**). In addition, substrates containing a heteroaryl (e.g. pyridinyl, thiophene, carbolines) also provided the desired products (Table 3, entries **2m-p**). Similar to the previous observation that functional groups containing acidic protons did not interfere the desired cyclopropanation (Table 2, **4q-s**), an unprotected carboxylic acid and α–carbolines also led to the corresponding cyclopropanation product in excellent yield (Table 3, **2j** and **2p**).

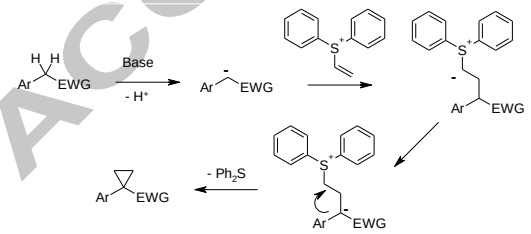
Furthermore, 1,3-dicarbonyl substrates were explored as shown in Table 4. The reactions proceeded efficiently for both aryl- (Table 4, **5a**) and alkyl-containing substrates (Table 4, **5b**), as well as diethyl malonate (Table 4, **5c**).

Table 4. Reaction scope for the cyclopropylation of 1,3-dicarbonyls.[a,b]



[a]Reagents and conditions: **3** (1 mmol), **A** (1.2 mmol), DBU (3 mmol), DMSO (5 mL), 21 °C, 12 h; [b]Isolated yield.

Based on the above results and literature reports,[9] a mechanism was proposed for the cyclopropanation of an aryl acetate (Scheme 3). Presumably, the substrate first undergoes deprotonation in the presence of DBU, followed by conjugate addition to the vinyl sulfonium salt. The subsequent 1,3-proton shift and intramolecular S_N2 reaction to expel phenyl sulphide from the zwitterionic intermediate affords the cyclopropanation product.



Scheme 3. The proposed mechanism for cyclopropanation of an aryl acetate using vinyl sulfonium salt.

Summary

In conclusion, a highly efficient cyclopropanation reaction was developed for the cyclopropanation of aryl or heteroaryl acetates, acetonitriles, and 1,3-dicarbonyl compounds using commercially available vinyl diphenyl sulfonium triflate. The reactions proceed under ambient conditions to provide the desired cyclopropanation products in high yields. The simple and mild reaction conditions, no requirement for an inert atmosphere or alkali bases, and the remarkable compatibility with a broad range of functional groups, demonstrate the potential of this reaction as a versatile method to generate aryl or heteroaryl acetates or acetonitriles containing a cyclopropyl moiety at the alpha position. As such, this method appears suitable for wide-spread application in medicinal chemistry.

Acknowledgments

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Supplementary data

Supplementary data associated with this article can be found, in the online version.

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- Highly efficient cyclopropanation of aryl and heteroaryl acetates and acetonitriles, as well as dicarbonyl compounds
- Convenient reaction protocol devoid of the use of strong base
- Reaction compatible with various functional groups such as carboxylic acid, boronic acid, amine, and carbamate
- Potential wide application in medicinal chemistry

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