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Brønsted Acid or Solid Acid Catalyzed Aza-Diels–Alder Reactions of Methylenecyclopropanes with Ethyl (Arylimino)acetates

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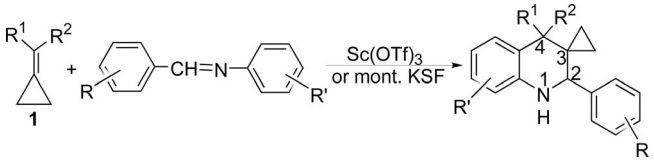
Brønsted acid (TfOH) or solid acid (montmorillonite K-10) catalyzed aza-Diels–Alder reactions of methylenecyclopropanes with ethyl (arylimino)acetates were shown for the construction of the tetrahydroquinoline skeleton with the untouched cyclopropyl group in the 3,3′-position.

Introduction

N-Heterocyclic compounds have attracted considerable attention from organic chemists owing to their functionality in pharmaceutical chemistry, material chemistry, synthetic organic chemistry, and dyes.[1] Among them, the greatest interest in 1,2,3,4-tetrahydroquinolines is due to their biological activities. Numerous tetrahydroquinolines bearing various simple or complex substituents have interesting biochemical activities; some of them are potential pharmaceutical agents.[2] With regard to the synthesis of a quinoline ring, various methods have been reported to date, such as the Skraup synthesis,[3] the Friedländer synthesis,[4] the Pfitzinger synthesis,[5] and so on.[6] However, to the best of our knowledge, less attention has been focused on the [4+2] cycloaddition reaction for the synthesis of a quinoline ring, although the reactions of *o*-quinone methide imines with olefins have recently appeared.[7,8] Chemical modification of natural compounds has become a commonly used approach for the formation of novel biologically active molecules with different pharmacological characteristics. Although the cyclopropane ring is a highly strained entity, it is nonetheless found in a wide variety of naturally occurring compounds[9] including terpenes,[10] pheromones,[11] fatty acid metabolites,[12] and unusual amino acids.[13] In addition, the rigidity of the three-membered ring renders this group an appealing structural unit for the preparation of molecules with a defined orientation of the pendant functional groups.[14]

Methylenecyclopropanes (MCPs) are highly strained but readily accessible molecules that have served as useful building blocks in organic synthesis.[15,16] Previously, we reported facile routes for the formation of tetrahydroquinoline derivatives with a cyclopropyl group in the 3,3′-position by Lewis acid catalyzed aza-Diels–Alder reactions of MCPs with *N*-aryl imines[17] or by solid acid montmorillonite KSF (mont. KSF) catalyzed one-pot, three-component, aza-Diels–Alder reactions of MCPs with aryl aldehydes and arylamines (Scheme 1).[18] These results promoted us to further investigate the cycloaddition reactions of MCPs with other types of imines. In this article, we will report our recent results on the Brønsted acid trifluoromethanesulfonic acid (TfOH) or solid acid montmorillonite K-10 (mont. K-10) catalyzed aza-Diels–Alder reactions of MCPs **1** with (arylimino)acetates **2** for the formation of tetrahydroquinoline skeletons.



Scheme 1. Lewis acid or solid acid catalyzed reactions of MCPs **1** with *N*-aryl imines.

Results and Discussion

Firstly, the reactions of MCP **1a** ($R^1 = R^2 = C_6H_5$) and (arylimino)acetate **2a** (R^3 = 4-Br) were carried out in 1,2-dichloroethane (DCE) in the presence of various Lewis acids (10 mol-%) or Brønsted acid (10 mol-%) at 5 °C. We

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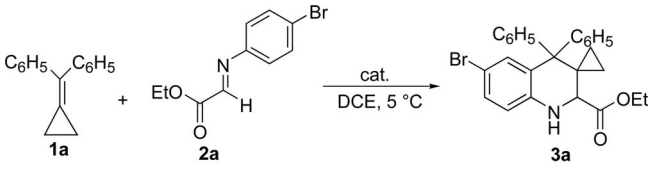
found that the reactions proceeded smoothly to give the aza-Diels–Alder reaction product, the corresponding tetrahydroquinoline derivative **3a**, in good yields for all the catalysts screened (Table 1, Entries 2–11). However, no reaction occurred in the absence of any catalyst (Table 1, Entry 1). It was found that the TfOH Brønsted acid gave the best result and the corresponding cycloaddition product was obtained in 82% yield within 0.5 h (Table 1, Entry 4). As for the solvents examined, DCE, compared with tetrahydrofuran (THF), toluene, and CH_3CN, DCE gave the best result for the TfOH-catalyzed aza-Diels–Alder reaction of MCP **1a** with (arylimino)acetate **2a** (Table 1, Entries 4 and 12–14).

Table 1. Optimization for the Lewis acid or Brønsted acid catalyzed reactions of MCP **1a** with (arylimino)acetate **2a**.



Entry[a]	Catalyst	Time [h]	Yield [%][b]
1	–	21	–
2	$Yb(OTf)_3$	3	71
3	$Cu(OTf)_2$	3	70
4	TfOH	0.5	82
5	$BF_3{\cdot}OEt_2$	3	71
6	$Sn(OTf)_2$	3	75
7	$La(OTf)_3$	8	71
8	$Zr(OTf)_4$	3	78
9	$Zn(OTf)_2$	19	72
10	$C_8F_{17}SO_3H$	19	77
11	$Sc(OPf)_3$ [$Sc(OSO_2C_8F_{17})_3$]	19	72
12[c]	TfOH	3	79
13[d]	TfOH	3	64
14[e]	TfOH	3	39

[a] Unless otherwise specified, all reactions were carried out by using **1a** (0.3 mmol), **2a** (0.3 mmol) in DCE (1 mL) at 5 °C for the listed catalyst (10 mol-%) and time. [b] Isolated yields. [c] THF as the solvent. [d] Toluene as the solvent. [e] CH_3CN as the solvent.

Then, we investigated the generality of the aza-Diels–Alder reactions of MCPs **1** with (arylimino)acetate **2a** under the optimized conditions. In most cases, the corresponding cycloaddition products were obtained in good to high yields within 0.5 h (Table 2, Entries 1–8). Electron-donating or electron-withdrawing substituents (R^1 and R^2) on the phenyl ring of MCPs **1** did not significantly affect these reaction outcomes (Table 2, Entries 1–8). As for the reactions involving unsymmetrical MCPs **1** such as **1e**, **1f**, **1g**, and **1i**, products **3e**, **3f**, **3g**, and **3n** were obtained as mixtures of *cis*/*trans* isomers (Table 2, Entries 4–6 and 8). As for products **3e** and **3n**, the two isomers could not be isolated by silica-gel column chromatography and their ratios were determined by ^1H NMR spectroscopy (Table 2, Entries 4 and 8) (see Supporting Information for details). The isomers of products **3f** and **3g** could be isolated by careful flash column chromatography (Table 2, Entries 5 and 6).[19] In the case of MCP **1j**, no such cycloaddition reaction could take place under the same conditions, presumably as a result of the steric hindrance of the substituent on the MCP (Table 2, Entry 9). The use of 4-nitrophenyl MCP **1k** as the substrate did not produce the desired aza-Diels–Alder reaction product (Table 2, Entry 10).

Table 2. Aza-Diels–Alder reactions of MCPs **1** with (arylimino)acetate **2a** catalyzed by TfOH.

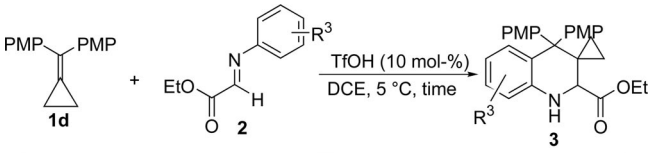
Entry[a]	**1** (R^1/R^2)	Yield [%][b] (*cis*/*trans*)
1	**1b** (4-MeC_6H_4/4-MeC_6H_4)	**3b**, 89
2	**1c** (4-FC_6H_4/4-FC_6H_4)	**3c**, 95
3	**1d** (4-$MeOC_6H_4$/4-$MeOC_6H_4$)	**3d**, 99
4	**1e** (4-$MeOC_6H_4$/C_6H_5)	**3e**, 92 (1:1)[c]
5	**1f** (4-$MeOC_6H_4$/H)	**3f**, 86 (67:19)[d]
6	**1g** (4-$MeOC_6H_4$/Me)	**3g**, 68 (39:29)[d]
7	**1h** (4-ClC_6H_4/4-ClC_6H_4)	**3m**, 81
8	**1i** (4-ClC_6H_4/C_6H_5)	**3n**, 92 (1:1)[c]
9	**1j** (2-ClC_6H_4/4-ClC_6H_4)	–
10	**1k** (4-$O_2NC_6H_4$/H)	–

[a] All reactions were carried out by using **1** (0.3 mmol) and **2a** (0.3 mmol) catalyzed by TfOH (10 mol-%) in DCE for 0.5 h. [b] Isolated yields. [c] Ratio of the isomers determined by ^1H NMR spectroscopy (see Supporting Information for details). [d] The isomers can be isolated by silica-gel column chromatography.

By using MCP **1d** as the substrate, we also examined its reactions with various (arylimino)acetates **2** under identical reaction conditions. All reactions took place smoothly to give products **3** in good to high yields within 10–30 min (Table 3). Substituents on the phenyl ring of (arylimino)acetates **2** have some effects on the reaction outcome. For example, (arylimino)acetate **2b** containing a strongly electron-donating group (R^3 = 4-MeO) afforded the corresponding adduct in almost quantitative yield, and the reaction was complete within 10 min (Table 3, Entry 1). The reaction rate was slightly retarded when an *ortho*-electron-withdrawing group on the phenyl ring was present, as (arylimino)acetate **2f** afforded **3l** in a somewhat lower yield (Table 3, Entry 5).

At the same time, we also examined the solvent effect on the reaction of MCP **1a** with (arylimino)acetate **2a** in the presence of solid acid mont. K-10. The aza-Diels–Alder reaction using DCE as the solvent at room temperature provided 88% yield of tetrahydroquinoline derivative **3a** within 3 h (Table 4, Entry 1).By using THF as the solvent, the reaction became disordered and no desired product was obtained (Table 4, Entry 2), which may be due to the fact that the oxygen atom in THF can coordinate to the active site in mont. K-10 clay and subsequently impair its catalytic ability in the reaction. Only some lower yields were found

Table 3. TfOH-catalyzed aza-Diels–Alder reactions of MCP **1d** with various (arylimino)acetates **2**.

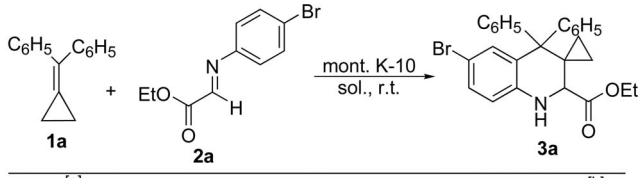


Entry[a]	**2** (R^3)	Time [min]	Yield [%][b]
1	**2b** (4-OMe)	10	**3h**, 99
2	**2c** (4-Cl)	30	**3i**, 86
3	**2d** (3-Me)	10	**3j**, 88
4	**2e** (H)	10	**3k**, 76
5	**2f** (2-Cl)	30	**3l**, 76

[a] All reactions were carried out with **1d** (0.3 mmol) and **2** (0.3 mmol) catalyzed by TfOH (10 mol-%) in DCE (1 mL) at 5 °C for the listed time. [b] Isolated yields.

if toluene and CH_3CN were used as the solvent (Table 4, Entries 3 and 4). The recovered solid acid catalyst (mont. K-10) can be reused to give similar results (Table 4, Entries 5 and 6). Other solid acids such as mont. KSF only gave 70% yield of the product for the same reaction and zeolite and silica gel showed no catalytic activities in this reaction (Table 4, Entries 7–9).

Table 4. Optimization of the mont. K-10 catalyzed reactions of MCP **1a** with (arylimino)acetate **2a**.



Entry[a]	Solvent	Time [h]	Yield [%][b]
1	DCE	3	88
2	THF	8	disordered
3	toluene	3	80
4	CH_3CN	3	81
5[c]	DCE	3	86
6[d]	DCE	3	86
7[e]	DCE	24	70
8[f]	DCE	3	trace
9[g]	DCE	3	trace

[a] Unless otherwise specified, all reactions were carried out by using **1a** (0.3 mmol), **2a** (0.3 mmol) catalyzed by mont. K-10 (50 mg) in the presence of the listed solvent (1 mL) at room temperature. [b] Isolated yields. [c] The recovered mont. K-10 was used for a second round. [d] The recovered mont. K-10 was used for a third round. [e] Mont. KSF was used as the catalyst. [f] Zeolite was used as the catalyst. [g] SiO_2 was used as the catalyst.

Having established the optimized reaction conditions involving the use of solid acid mont. K-10 as the catalyst, various MCPs **1** and (arylimino)acetate **2a** were subjected to the reaction to examine the feasibility of the methodology. All reactions were complete within 3 h at room temperature to give cycloaddition products **3** in excellent yields (Table 5). To our delight, the yields were generally higher than those catalyzed by the TfOH Brønsted acid (Table 2 and Table 5).

Table 5. Mont. K-10 catalyzed reactions of MCPs **1** with (arylimino)acetate **2a**.

Entry[a]	**1** (R^1/R^2)	Yield [%][b] (*cis*/*trans*)
1	**1b** (4-MeC_6H_4/4-MeC_6H_4)	**3b**, 91
2	**1c** (4-FC_6H_4/4-FC_6H_4)	**3c**, 97
3	**1d** (4-$MeOC_6H_4$/4-$MeOC_6H_4$)	**3d**, 95
4	**1e** (4-$MeOC_6H_4$/C_6H_5)	**3e**, 99 (1:1)[c]
5	**1f** (4-$MeOC_6H_4$/H)	**3f**, 95 (58:37)[d]
6	**1g** (4-$MeOC_6H_4$/Me)	**3g**, 97 (55:42)[d]
7	**1h** (4-ClC_6H_4/4-ClC_6H_4)	**3m**, 99
8	**1i** (4-ClC_6H_4/C_6H_5)	**3n**, 99 (1:1)[c]
9	**1j** (2-ClC_6H_4/4-ClC_6H_4)	–
10	**1k** (4-$O_2NC_6H_4$/H)	–

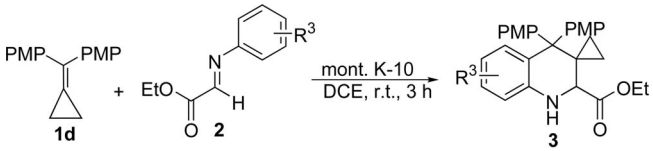
[a] All reactions were carried out with **1** (0.3 mmol) and **2a** (0.3 mmol) catalyzed by mont. K-10 (50 mg) in DCE (1.0 mL) at room temperature for 3 h. [b] Isolated yields. [c] Ratio of the isomers determined by ^1H NMR spectroscopy (see Supporting Information for details). [d] The isomers can be isolated by silica-gel column chromatography.

The reactions of MCP **1d** with various (arylimino)acetates **2** were also investigated to further examine the generality of the reaction under identical reaction conditions. Although a reaction time of 3 h was required, the yields of the corresponding aza-Diels–Alder reactions catalyzed by mont. K-10 were higher than those catalyzed by TfOH in most cases (Table 3 and Table 6).

It should be mentioned that for bis(alkyl)-substituted MCPs **1** (R^1, R^2 = alkyl group) or (alkylimino)acetates **2** derived from aliphatic amines, neither Brønsted acid nor solid acid showed catalytic activity for the corresponding aza-Diels–Alder reactions. This is because the stepwise aza-Diels–Alder reaction of (bis)alkyl-substituted MCPs with imines under the same conditions cannot stabilize a cationic intermediate, which should be generated during the reaction.[17]

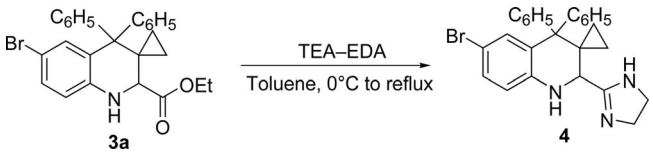
The ester group of the aza-Diels–Alder reaction products can be converted into other functional groups by simple reported operations. For example, product **3a** can be easily converted into corresponding imidazoline derivative **4** in 60% yield by triethylaluminum (TEA) and ethane-1,2-diamine (EDA) in toluene under reflux for 45 min, which is structurally analogous to some compounds with potential pharmaceutical activities (Scheme 2).[20]

Table 6. Mont. K-10 catalyzed reactions of MCP **1d** with (arylimino)acetates **2**.



Entry[a]	**2** (R^3)	Yield [%][a]
1	**2b** (4-OMe)	**3h**, 99
2	**2c** (4-Cl)	**3i**, 99
3	**2d** (3-Me)	**3j**, 79
4	**2e** (H)	**3k**, 92
5	**2f** (2-Cl)	**3l**, 82

[a] All reactions were carried out with **1d** (0.3 mmol) and **2** (0.3 mmol) catalyzed by mont. K-10 (50 mg) in DCE (1 mL) at room temperature for 3 h. [b] Isolated yields.



Scheme 2. Conversion of compound **3a**.

Conclusions

In conclusion, we have disclosed two facile routes for the formation of the tetrahydroquinoline skeleton with a cyclopropyl group in the 3,3′-position. As a result of the potential pharmaceutical applications of this tetrahydroquinoline skeleton containing a highly strained cyclopropyl-ring substituent, these new compounds may find some usefulness in the near future. Biological activity tests are underway in the National Center for Drug Screening.

Experimental Section

General Procedure for the TfOH-Catalyzed Reactions of MCPs 1 with Ethyl (Arylimino)acetates 2: Under an argon atmosphere, **2a** (76.8 mg, 0.3 mmol), **1a** (61.8 mg, 0.3 mmol), TfOH (3 μL, 0.03 mmol, 10 mol-%), and DCE (1.0 mL) were added into a Schlenk reaction tube. The mixture was stirred at 5 °C for 0.5 h, then quenched by the addition of solid sodium hydrogen carbonate. The solvent was removed under reduced pressure, and the residue was purified by flash column chromatography (SiO_2) to give **3a** in 82% yield (113 mg).

General Procedure for the Mont. K-10 Catalyzed Reactions of MCPs 1 with Ethyl (Arylimino)acetates 2: Under an argon atmosphere, **2a** (76.8 mg, 0.3 mmol), **1a** (61.8 mg, 0.3 mmol), mont. K-10 (50 mg), and DCE (1.0 mL) were added into a Schlenk reaction tube. The mixture was stirred at room temperature for 3 h. The solvent was removed under reduced pressure, and the residue was purified by flash column chromatography (SiO_2) to give **3a** in 82% yield (122 mg).

Compound 3a: White solid, m.p. 176–177 °C. IR (CH_2Cl_2): $\tilde{\nu}$ = 3397, 3054, 2979, 2899, 1732, 1711, 1595, 1489, 1442, 1365, 1291, 1203, 1123, 1082, 1030, 873, 807, 754, 702 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$, TMS): δ = 0.45–0.56 (m, 3 H), 1.04–1.07 (m, 1 H), 1.25 (t, J = 6.9 Hz, 3 H, CH_3), 4.06–4.12 (m, 2 H), 4.36 (s, 1 H), 4.51 (s, 1 H, NH), 6.55 (d, J = 8.4 Hz, 1 H, Ar), 6.99–7.04 (m, 3 H, Ar), 7.16–7.27 (m, 5 H, Ar), 7.32–7.37 (m, 2 H, Ar), 7.53 (d, J = 8.4 Hz, 2 H, Ar) ppm. ^{13}C NMR (75 MHz, $CDCl_3$, TMS): δ = 4.5, 8.9, 14.1, 23.4, 56.0, 58.1, 61.4, 108.1, 117.3, 126.6, 126.77, 126.81, 128.8, 129.7, 130.4, 131.3, 134.6, 141.9, 142.2, 143.0, 145.2, 171.7 ppm. MS (EI): m/z (%) = 463 (43), 462 (13), 461 $[M]^+$ (44), 390 (94), 389 (25), 388 (100), 310 (24), 309 (41), 210 (58), 208 (61). $C_{26}H_{24}BrNO_2$ (461.10): calcd. C 67.54, H 5.23, N 3.03; found C 67.26, H 5.08, N 2.91.

Supporting Information (see footnote on the first page of this article): Detailed experimental procedures and spectroscopic data.

Acknowledgments

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