Montmorillonite KSF-Catalyzed One-Pot, Three-Component, Aza-Diels–Alder Reactions of Methylenecyclopropanes with Arenecarbaldehydes and Arylamines

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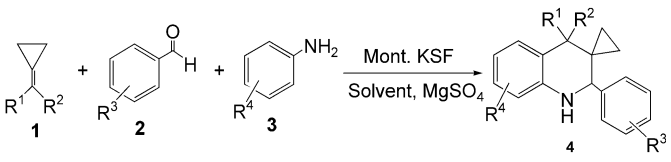
Supporting Information for this article is available on the WWW under http://asc.wiley-vch.de or from the author.

Abstract: A series of novel quinoline derivatives having a spirocyclopropyl ring can be synthesized by one-pot, three-component aza-Diels–Alder reactions of arenecarbaldehydes, arylamines, and methylenecyclopropanes (MCPs) using a heterogeneous solid acid catalyst, montmorillonite KSF, under mild reaction conditions in good to excellent yields.

Keywords: arenecarbaldehydes; arenes; arylamines; aza-Diels–Alder reaction; clays; methylenecyclopropanes; heterogeneous solid acid catalysts; montmorillonite KSF; quinolines

During our investigations on the transformations of methylenecyclopropanes **1** (MCPs) catalyzed by Lewis acids,[1,2] we disclosed a previously unknown transformation process of MCPs by the reaction with imines in the presence of lanthanide triflates $Ln(OTf)_3$ (Lewis acids) to give aza-Diels–Alder products in good to excellent yields.[3a,3b–f] A range of imines derived from arenecarbaldehydes **2** and arylamines **3** has been examined. This process provides a novel and efficient route to the synthesis of quinoline derivatives having a cyclopropyl ring. However, the synthesis of imines from various arenecarbaldehydes **2** and arylamines **3** and the use of expensive lanthanide triflates are required in this process. In general, imines are unstable compounds which are easily decomposed to the starting materials aldehydes and amines in the presence of water. Recently, the one-pot multi-component synthetic procedure[4] and the use of solid acid catalysts such as clays and zeolites[5] have attracted considerable attention in different areas of organic synthesis which can largely simplify the synthetic step and operation under environmentally benign conditions.[6] Since the one-pot treatment using arenecarbaldehydes **2** and arylamines **3** has been disclosed before for the synthesis of homoallylic amines[7,8] instead of imines, herein we describe a simple and efficient synthesis of quinoline derivatives having a cyclopropyl group in a one-pot, three-component manner using a heterogeneous solid acid catalyst, montmorillonite KSF clay, under mild reaction conditions (Scheme 1).

The reaction of di(*p*-methoxyphenyl)methylenecyclopropane **1a** (0.1 mmol), benzaldehyde **2a** (0.1 mmol), and *m*-trifluoromethylaniline **3a** (0.1 mmol) was carried out in the presence of montmorillonite KSF clay (50 mg) in various solvents under the ambient atmosphere. In order to get rid of the produced water during the reaction, anhydrous $MgSO_4$ (0.15 mmol) was employed in this reaction system. This one-pot, three-component reaction was performed in a heterogeneous phase. The results are summarized in Table 1. As can be seen from Table 1, the reaction proceeded very well in CH_3CN or CH_2Cl_2 (DCM) to give the corresponding aza-Diels–Alder adduct **4a** in very high yields (Table 1, entries 1 and 2). When the reaction was carried out in ethanol or 1,2-dichloroethane (DCE) or ethyl acetate, the aza-Diels–Alder adduct **4a** was obtained in moderate yields (Table 1, entries 3, 7, and 9). But, if the reaction was performed in acetone, ether, toluene or THF, the aza-Diels–Alder adduct **4a** was produced in very low yields (Table 1, entries 4, 5, 6, and 8). This may be due to that the oxygen atom in acetone, ether or THF can coordinate to the active site in montmorillonite KSF clay and subsequently impair its catalytic ability in the reaction. However, in the case of ethanol and ethyl acetate, the oxygen atoms do not have a strong coordination effect owing to their structures. Toluene is a non-polar solvent



Scheme 1.

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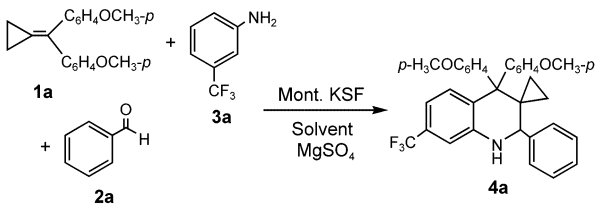
Table 1. The effects of various solvents in the reaction of MCP (**1a**) with arenecarbaldehyde (**2a**) and arylamine (**3a**) catalyzed by KSF.



Entry	Solvent	Time [h]	Yield [%][a]
1	CH_3CN	10	100
2	CH_2Cl_2	24	90
3	$ClCH_2CH_2Cl$	32	59
4	Acetone	36	Trace
5	THF	40	Trace
6	Et_2O	40	<20
7	EtOH	75	64
8	Toluene	75	Trace
9	EtOAc	36	54
10[b]	CH_3CN	10	100
11[b]	CH_3CN	10	100
12[c]	CH_3CN	24	NR
13[d]	CH_3CN	24	NR
14[e]	CH_3CN	24	NR

[a] Isolated yields.
[b] The catalyst (KSF and $MgSO_4$) recovered by filtration from the reaction mixture was used as the catalyst after drying at 120 °C for 4 h in an oven.
[c] Silica gel (SiO_2) was used as the catalyst.
[d] Zeolite was used as the catalyst.
[e] Neutral Al_2O_3 was used as the catalyst.

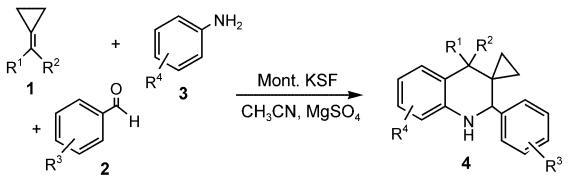
which cannot accelerate this one-pot, three-component coupling reaction. Thus, the best solvent is CH_3CN. It should be noted that the montmorillonite KSF clay can be recovered with $MgSO_4$ after reaction just by filtration. The recovered solid acid catalyst (KSF and $MgSO_4$) can be reused in the next reaction to give the same results (Table 1, entries 10 and 11). The other solid acid catalysts such as silica gel (SiO_2), neutral Al_2O_3, and zeolite showed no catalytic abilities for this reaction (Table 1, entries 12, 13, and 14).

Under the optimized reaction conditions, we then carried out this one-pot, three-component aza-Diels–Alder reaction using other substrates. The results are summarized in Table 2. As can be seen from Table 1, for MCPs **1** in which either R^1 and R^2 are aryl groups such as **1a**, **1d** and **1e**, or R^1 is aryl group and R^2 is aliphatic group such as **1c**, the reaction can take place to give the corresponding aza-Diels–Alder product **4**. We also found that the electron-donating or electron-withdrawing substituents on the benzene ring (R^1 and/or R^2) of MCPs **1** significantly affected this reaction. If R^1 and/or R^2 of MCPs **1** having electron-donating substituents such as MeO or EtO group on the benzene ring, this aza-Diels–Alder reaction proceeded very well to give the corresponding adducts **4** in high yields under the same conditions (Table 2, entries 1 – 10 and 13). Using diphenylmethylenecyclopropane **1b** as the substrate, the reaction became sluggish. Thus, we did not use **1b** as a substrate for this reaction. For arylamines **3** either having electron-donating or electron-withdrawing groups on the benzene ring, the aza-Diels–Alder products **4** are obtained in good to very high yields under the same conditions (Table 2). On the other hand, for arenecarbaldehydes **2**, the electronic properties of substituents on the benzene ring do not significantly affect the reaction because in the reactions of MCP **1a** and *p*-nitrobenzaldehyde **2d** having a strongly electron-withdrawing group with aniline and MCP **1c** and *p*-methoxybenzaldehyde **2b** having a strongly electron-donating group with aniline catalyzed by KSF under the same conditions, the corresponding aza-Diels–Alder adducts **4 l** and **4 m** were obtained in 32% and 44%, respectively (Table 2, entries 11 and 12). These results suggest that the combination of three components in this reaction system is very important in order to produce the coupling adducts in high yields.

In the reactions of unsymmetric MCP **1c** (monoalkyl-substituted MCPs) with arenecarbaldehydes and arylamines under the same conditions, the aza-Diels-Alder product was given as a *cis*- and *trans*-mixture (Table 2, entries 2, 3, 5, 8, and 12). The ratios of *cis*-**3** and *trans*-**3** were determined based on the ^1H NMR spectroscopic data (Please see supporting information).[9] It should be mentioned that for aliphatic amines or bisalkylated MCPs (R^1 and R^2=aliphatic group), no reactions occurred.

In conclusion, we have disclosed a previously unknown transformation process of MCPs **1** by a one-pot, three-component synthetic method with arenecarbaldehydes **2** and arylamines **3** in the presence of a very cheap solid acid montmorillonite KSF clay to give aza-Diels–Alder products **4** in good to excellent yields under mild conditions. A range of arylamines and arenecarbaldehydes has been examined. This process provides a novel and efficient route to the synthesis of quinoline derivatives having a cyclopropyl ring. Efforts are underway to elucidate the further mechanistic details of this reaction and to identify systems enabling similar reactions of other substrates and subsequent transformations thereof.

Table 2. Montmorillonite KSF-catalyzed one-pot, three-component aza-Diels–Alder reactions of MCPs **1** with arenecarbaldehydes and arylamines.



1a: $R^1 = R^2 = p\text{-}CH_3OC_6H_4$; **1b**: $R^1 = R^2 = C_6H_5$;
1c: $R^1 = p\text{-}EtOC_6H_4$, $R^2 = CH_3$;
1d: $R^1 = R^2 = p\text{-}CH_3C_6H_4$; **1e**: $R^1 = p\text{-}CH_3OC_6H_4$, $R^2 = C_6H_5$.
2a: R^3 = H; **2b**: $R^3 = p\text{-}CH_3O$; **2c**: $R^3 = p$-Cl; **2d**: $R^3 = p\text{-}NO_2$.
3a: $R^4 = m\text{-}CF_3$; **3b**: R^4 = H; **3c**: $R^4 = o\text{-}CH_3O$; **3d**: $R^4 = p$-EtO.

Entry	MCP	Aldehyde	Amine	Time [h]	Product	Yield [%][a] (*cis*/*trans*)
1	**1a**	**2a**	**3b**	40	**4b**	100
2	**1c**	**2a**	**3b**	36	**4c**	100 (3/2)
3	**1c**	**2a**	**3a**	24	**4d**	100 (10/1)
4	**1d**	**2a**	**3a**	64	**4e**	100
5	**1c**	**2a**	**3c**	64	**4f**	98 (2/1)
6	**1a**	**2b**	**3b**	36	**4g**	67
7	**1a**	**2a**	**3d**	48	**4h**	100
8	**1c**	**2a**	**3d**	48	**4i**	100 (3/1)
9	**1e**	**2c**	**3b**	40	**4j**	81 (5/1)
10	**1a**	**2c**	**3b**	35	**4k**	98
11	**1a**	**2d**	**3b**	27	**4l**	32
12	**1c**	**2b**	**3b**	64	**4m**	44 (3/1)
13	**1e**	**2d**	**3d**	40	**4n**	89 (2/1)

[a] Isolated yields.

Experimental Section

General Remarks

^{1}H NMR spectra were recorded on a 300 MHz spectrometer in $CDCl_3$ using tetramethylsilane as an internal standard. Infrared spectra were measured on a Perkin-Elmer 983 spectrometer. Mass spectra were recorded with an HP-5989 instrument and HRMS was measured by a Finnigan MA+ mass spectrometer. Satisfactory CHN microanalyses were obtained with a Carlo-Erba 1106 analyzer. Melting points are uncorrected. All reactions were monitored by TLC with Huanghai GF_{254} silica gel coated plates. Flash column chromatography was carried out using 300–400 mesh silica gel.

General Procedure

Under the ambient atmosphere, arenecarbaldehyde **2a** (10.6 mg, 0.1 mmol), arylamine **3a** (16.1 mg, 0.1 mmol), anhydrous $MgSO_4$ (18 mg, 0.15 mmol) and acetonitrile (1.0 mL) were added into a Schlenk tube. After the reaction mixture had been stirred for about 2.0 h at room temperature, MCP **1a** (26.4 mg, 0.1 mmol) and Montmorillonite KSF (50 mg) were added successively. The reaction mixture was stirred at room temperature for several hours. The solvent was removed under reduced pressure and the residue was purified by silica gel column chromatography (SiO_2, eluent: petroleum ether/EtOAc, 20/1) to give **4a** as a white solid; yield: 51 mg (100%).

General Procedure for Recycling the Catalyst

When the reaction was completed, the reaction mixture was filtered off and the solid was washed with dimethoxyethylene (DME). The obtained solid (KSF and $MgSO_4$) was dried at 120 °C in an oven for 4 hours. The recovered solid was directly used for the next one-pot, three-component reaction of **1a**, **2a**, and **3a** without additional $MgSO_4$. The yields of the corresponding aza-Diels–Alder adduct **4a** were almost same for two runs by the same recovered catalyst.

7-Trifluoromethyl-4,4-bis(4-methoxyphenyl)-2-phenyl-1,2,3,4-tetrahydrospiro(3,1′-cyclopropyl)quinoline (4a): White solid; mp 168–170 °C; ^{1}H NMR ($CDCl_3$, 300 MHz, TMS): $\delta =$ 0.25–0.29 (m, 4H), 3.76 (s, 3H, OCH_3), 3.86 (s, 3H, OCH_3), 4.30 (s, 1H, NH), 5.11 (s, 1H), 6.70 (d, 2H, $J = 9.0$ Hz, Ar), 6.88–6.98 (m, 6H, Ar), 7.08 (d, 1H, $J = 8.4$ Hz, Ar), 7.31–7.34 (m, 5H, Ar), 7.54 (d, 2H, $J = 8.4$ Hz, Ar); ^{13}C NMR ($CDCl_3$, 75 MHz, TMS): $\delta = 7.22$, 25.44, 29.66, 53.39, 55.08, 55.54, 58.02, 112.19, 112.58, 114.08, 124.62 (q, $J_{C\text{-}F} = 270$ Hz), 128.24 (q, $J_{C\text{-}F} =$ 29.7 Hz), 129.28, 129.70, 130.12, 130.72, 131.61, 131.64 (q, $J_{C\text{-}F} = 4.8$ Hz), 133.06, 133.41, 135.20, 139.74, 139.96, 146.32, 158.17, 158.23; IR (CH_2Cl_2): $\nu = 3378$, 3002, 2929, 2837, 1713, 1606, 1507, 1251, 831, 752, 705 cm^{-1}; MS: *m/e* (%) = 515 (M^+, 3.73), 406 (100); HRMS: calcd. for $C_{32}H_{28}F_3NO_2$: 515.2072; found: 515.2050; anal. calcd. for $C_{32}H_{28}F_3NO_2$: C 74.55%, H 5.47%, N 2.72%; found: C 74.48%, H 5.63%, N 2.58%.

Acknowledgements

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References and Notes

[1] For a recent review: I. Nakamura, Y. Yamamoto, *Adv. Synth. Catal.* **2002**, *2*, 111–129; for the synthesis of MCPs: A. Brandi, A. Goti, *Chem. Rev.* **1998**, *98*, 589–635.

[2] a) The Lewis acid-catalyzed ring-opening reactions of MCPs: M. Shi, B. Xu, *Org. Lett.* **2002**, *4*, 2145–2148 and references cited therein; b) M. Shi, Y. Chen, B. Xu, J. Tang, *Tetrahedron Lett.* **2002**, *43*, 8019–8024; on the other hand, Kilburn reported Lewis acid mediated cascade reactions of silyl-substituted methylenecyclopropane with ketones and aldehydes: c) G. L. N. Peron, J. Kitteringham, J. D. Kilburn, *Tetrahedron Lett.* **2000**, *41*, 1615–1618; d) G. L. N. Peron, D. Norton, J. Kitteringham, J. D. Kilburn, *Tetrahedron Lett.* **2001**, *42*, 347–348; e) L.

Patient, M. B. Berry, J. D. Kilburn, *Tetrahedron Lett*. **2003**, *44*, 1015 – 1017.

[3] a) M. Shi, L.-X. Shao, B. Xu, *Org. Lett*., **2003**, *5*, 579 – 582; for more examples of the reactions of imines with simpler olefins, please see: b) S. Kobayashi, H. Ishitani, S. Nagayama, *Synthesis* **1995**, 1195 – 1199; c) J. S. Yadav, B. V. S. Reddy, C. R. Madhuri, G. Sabitha, *Synthesis* **2001**, 1065 – 1070; d) R. Nagarajan, P. T. Perumal, *Synth. Commun*. **2001**, *31*, 1733 – 1735; e) M. Anniyappan, R. Nagarajan, P. T. Perumal, *Synth. Commun*. **2002**, *32*, 99 – 101.

[4] a) J.-C. Gauffre, M. Grignon-Dubois, B. Rezzonico, J.-M. Léger, *J. Org. Chem*. **2002**, *67*, 4696 – 4701; b) P. J. Manley, M. J. Bilodeau, *Org. Lett*. **2002**, *4*, 3127 – 3129, c) F. Bertozzi, M. Gustafasson, R. Olsson, *Org. Lett*. **2002**, *4*, 3147 – 3150; d) R. Varala, M. M. Alam, S. R. Adapa, *Synlett* **2003**, 67 – 70; e) D. S. Bose, L. Fatina, H. B. Mereyala, *J. Org. Chem*. **2003**, *68*, 587 – 590.

[5] a) M. Balogh, P. Laszlo, *Organic Chemistry using Clays*, Springer Verlag, Berlin, **1993** and references cited therein; b) A. Cornelis, P. Laszlo, *Synlett* **1994**, 155 – 161; c) T. Akiyama, K. Matsuda, K. Fuchile, *Synlett* **2002**, 1898 – 1900; d) S. Samajdar, F. F. Becker, B. K. Banik, *Heterocycles*, **2001**, *55*, 1019 – 1022; e) A. Nasreen, *Synlett* **2001**, 1341 – 1342.

[6] For more examples using montmorillonite KSF as the catalyst in organic synthesis, please see: a) B. Labiad, D. Villemin, *Synthesis* **1989**, 143 – 144; b) W. G. Dauben, J. M. Cogen, V. Behar, *Tetrahedron Lett*. **1990**, *31*, 3241 – 3244; c) J. S. Yadav, B. V. S. Reddy, G. M. Kumar, Ch. V. S. R. Murthy, *Tetrahedron Lett*. **2001**, *42*, 89 – 91; d) H. M. S. Kumar, B. V. S. Reddy, P. K. Mohanty, J. S. Yadav, *Tetrahedron Lett*. **1997**, *38*, 3619 – 3622; e) H. M. S. Kumar, B. V. S. Reddy, S. Anjaneyulu, E. J. Reddy, J. S. Yadav, *New J. Chem.* **1999**, *23*, 955 – 956.

[7] a) S. Kobayashi, T. Busujima, S. Nagayama, *Chem. Commun*. **1998**, 19 – 20; b) S. Kobayashi, S. Nagayama, *J. Am. Chem. Soc*. **1996**, *118*, 6641 – 6647; c) H. C. Aspinall, J. S. Bissett, N. Greeves, D. Levin, *Tetrahedron Lett*. **2002**, *43*, 323 – 325 d) S. Kobayashi, S. Iwamoto, S. Nagayama, *Synlett* **1997**, 1099 – 1101; e) J. S. Yadav, B. V. S. Reddy, A. Krishnam Raju, D. Gnaneshwar, *Adv. Synth. Catal*. **2002**, *344*, 938 – 940.

[8] a) T. Akiyama, Y. Onuma, *J. Chem. Soc. Perkin Trans. 1* **2002**, 1157 – 1162; b) Y. Masuyama, J. Tosa, Y. Kurusu, *Chem. Commun*. **1999**, 1075 – 1076; c) T. Akiyama, J. Iwai, Y. Onuma, H. Kagoshima, *Chem. Commun*. **1999**, 2191 – 2192.

[9] The stereoisomers of *cis*-**4** and *trans*-**4** were determined based on the chemical shift of ^{1}H NMR spectroscopic data. Please see: H. Primke, G. S. Sarin, S. Kohlstruk, G. Adiwidjaja, A. de Meijere, *Chem. Ber*. **1994**, *127*, 1051 – 1064.

