CL-150896 Received: September 25, 2015 | Accepted: October 14, 2015 | Web Released: October 22, 2015

Pummerer Reaction of Sulfoxides in Acetic Anhydride Catalyzed by Al-MCM-41

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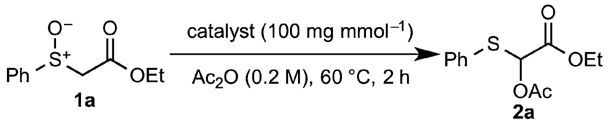
The Pummerer reaction of acetic anhydride with both alkyl aryl sulfoxides and dialkyl sulfoxides was efficiently promoted by a mesoporous aluminosilicate Al-MCM-41 to afford the corresponding α-acetoxy sulfides in high yields. The catalyst was easily recovered by filtration and could be reused three times without a significant loss of catalytic activity.

The Pummerer reaction involves the reaction of a nucleophile with a sulfonium ion generated from a sulfoxide to afford the corresponding α-substituted sulfide.[1] Many kinds of inter- and intramolecular Pummerer reactions have been developed, and the reaction is now recognized as a powerful tool for constructing the skeleton of natural products and biologically active compounds.[1,2] In many cases, acetic anhydride is used to activate a sulfoxide in the Pummerer reaction.[3] Typically, the reaction is performed under reflux in acetic anhydride, and the addition of several reagents such as sodium acetate,[3a,3b] trifluoroacetic anhydride,[3c] or *p*-toluenesulfonic acid[3d,3e] is effective to reduce side reactions and improve the yields. However, there has been no report on the Pummerer reaction of acetic anhydride with sulfoxides catalyzed by heterogeneous catalysts to the best of our knowledge. The development of the environmentally benign heterogeneous catalytic systems has become one of the most important themes in current organic chemistry.[4] Recently, aluminum-incorporated MCM-41 (Al-MCM-41) was reported as an attractive heterogeneous solid acid catalyst for several organic reactions because of their large uniform pores (2–10 nm) and high surface areas.[5] Although the catalytic activities of Al-MCM-41 are often comparable to that of amorphous silica–alumina,[5a,5b] it has been shown that Al-MCM-41 expresses much higher catalytic activities than amorphous silica–alumina.[5c–5f] However, the reported examples were limited to the reaction using silyl nucleophiles for the formation of carbon–carbon bond. Herein, we wish to report the remarkable catalytic activities of Al-MCM-41 in the Pummerer reaction to form a new carbon–oxygen bond.

Initially, Al-MCM-41 (Si/Al = 23) was synthesized by the known procedure with a slight modification,[6,7] and the catalytic activity of Al-MCM-41 was examined in the reaction of acetic anhydride with ethoxycarbonylmethyl phenyl sulfoxide (**1a**).[8] In the presence of Al-MCM-41 (100 mg mmol^{-1}), dried with a heating gun in vacuo prior to use, **1a** in acetic anhydride was stirred at 60 °C for 2 h. The catalyst was filtered off and the filtrate was evaporated to afford almost pure α-acetoxy sulfide **2a**. After silica-gel column chromatography, **2a** was isolated in 95% yield (Table 1, Entry 1).[9] Although the Pummerer reaction sometimes proceed by heating without any catalyst,[1a] the reaction did not take place at the same reaction conditions without Al-MCM-41 (Entry 2). The reaction was then examined by using a higher amount (270 mg mmol^{-1}) of amorphous silica–alumina (SiO_2–Al_2O_3, Si/Al = 31) to unify the surface areas of Al-MCM-41 and SiO_2–Al_2O_3. However, **2a** was obtained only in 6% yield (Entry 3). Furthermore, aluminum-free MCM-41 also gave the product in poor yield (Entry 4). These results suggest that high catalytic activity of Al-MCM-41 is achieved by the presence of both mesoporous structure and aluminum moiety in the catalyst, as was observed in the cases of Al-MCM-41-catalyzed reaction of silyl nucleophiles.[5c–5f] The use of a lower amount of Al-MCM-41 (30 mg mmol^{-1}) also afforded **2a** quantitatively, although the reaction required 8 h to complete (Entry 5).[11]

Table 1. Pummerer reaction of sulfoxide **1a**



Entry	Catalyst (Si/Al)	Specific surface area (BET) /m^2 g^{-1}	Yield/%[a]
1	Al-MCM-41 (23)	1032	>95 (95)[b]
2	none	—	0
3[c]	SiO_2–Al_2O_3 (31)	385	6
4	MCM-41 (–)	1080	<5
5[d]	Al-MCM-41 (23)	1032	>95

[a]Determined by ^{1}H NMR analysis of the crude product using bromoform as an internal standard. [b]Isolated yield. [c]SiO_2–Al_2O_3 (270 mg mmol^{-1}). [d]Al-MCM-41 (30 mg mmol^{-1}); reaction time was 8 h.

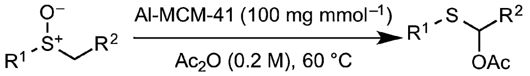
Table 2. Reuse of Al-MCM-41 in the reaction of acetic anhydride with **1a**[a]

Run	Al-MCM-41 /mg	**1a** /mmol	Time /h	Yield/%[b]
1	100	1.0	2	95
2	75	0.75	2	96
3	53	0.53	2	91
4	27	0.27	3	88

[a]In the presence of Al-MCM-41 (100 mg mmol^{-1}), **1a** in Ac_2O (0.2 M) was stirred at 60 °C. [b]Isolated yield.

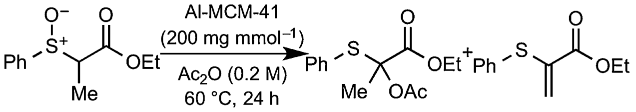
Next, the recovery and reuse of Al-MCM-41 were tested in the reaction of acetic anhydride with **1a** (Table 2).[12] The catalyst was recovered by filtration after the reaction. The recovered catalyst was then dried at 60 °C for 15 min, and treated in the same manner as the first run. As shown in Table 2, the catalyst could be reused three times, although the catalytic activity was slightly decreased after repeated use of the catalyst.

Table 3. Pummerer reaction of acetic anhydride with various sulfoxides catalyzed by Al-MCM-41



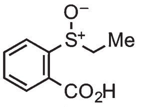
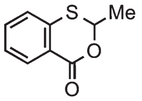
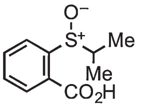
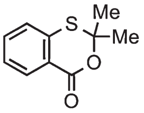
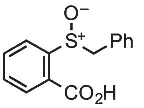
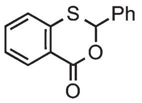
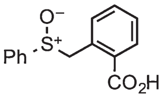
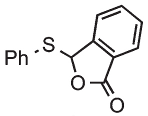
Entry	R^1	R^2	Time /h	Yield /%[a]
1	Ph	CN	2	96
2	Ph	PhCO	1	95
3[b]	Ph	4-BrC$_6$H$_4$CO	1	88
4	Ph	4-MeC$_6$H$_4$CO	1	91
5	Ph	4-MeOC$_6$H$_4$CO	1	85
6	Ph	Ac	0.5	91
7	4-BrC$_6$H$_4$	PhCO	1	88
8	4-MeC$_6$H$_4$	PhCO	1	92
9	4-MeOC$_6$H$_4$	PhCO	1	89
10	Ph	H	12	21
11[c]	Ph	H	12	91
12	Ph	Ph	12	<10
13[c]	Ph	Ph	10	13
14	Me	PhCO	1	82
15[b]	Bn	PhCO	0.5	94
16	Bn	CO$_2$Et	1	95

[a] Isolated yield. [b] Ac$_2$O (0.1 M). [c] Reaction was carried out at 100 °C.



Scheme 1. Al-MCM-41-catalyzed Pummerer reaction of **3**.

Table 4. Intramolecular Pummerer reaction catalyzed by Al-MCM-41[a]

Entry	Sulfoxide	Time /h	Product	Yield /%[b]
1	 **6a**	2	 **7a**	96
2	 **6b**	2	 **7b**	95
3	 **6c**	3	 **7c**	73
4	 **8**	8	 **9**	96

[a] Reaction conditions: sulfoxide (0.2 mmol), Ac$_2$O (1 mL), Al-MCM-41 (20 mg, Si/Al = 26), 60 °C (Entries 1–3) or 80 °C (Entry 4). [b] Isolated yield.

The scope of Al-MCM-41-catalyzed α-acetoxylation of various sulfoxides was then investigated (Table 3). Alkyl phenyl sulfoxides containing electron-withdrawing groups at the α-position of sulfoxide reacted quickly to give the corresponding α-acetoxy sulfides in good yields within 2 h (Entries 1–9). It is noted that the desired α-acetoxy sulfides were obtained from β-keto sulfoxides in this solid acid-catalyzed reaction (Entries 2–9) in contrast with the sodium acetate-promoted Pummerer reaction, which affords the thioester of α-acetoxy carboxylic acid from β-keto sulfoxides via α-acetoxy sulfides.[3b] The reaction of methyl phenyl sulfoxide was sluggish at 60 °C, but the desired product was obtained in high yield (91%) by stirring at 100 °C for 12 h (Entries 10 and 11). The reaction of benzyl phenyl sulfoxide was also sluggish, and the yield could not be improved by the decomposition of the product at higher temperatures (Entries 12 and 13). When dialkyl sulfoxides were used, the reaction took place regioselectively at the α-carbon with electron-withdrawing groups (Entries 14–16). In the case of α-disubstituted sulfoxide **3**, α-acetoxy sulfide **4** was obtained in 51% yield along with α,β-unsaturated sulfide **5** (26% yield), whereas it was reported that **5** was the major product when methanesulfonic acid was used in the reaction of **3** with acetic anhydride (Scheme 1).[3f]

The Al-MCM-41-catalyzed system was then applied to the intramolecular Pummerer reaction (Table 4). The reaction of alkyl 2-carboxyphenyl sulfoxide **6a**–**6c** in acetic anhydride at 60 °C gave the corresponding 4*H*-benzo[*d*][1,3]oxathiin-4-one derivatives **7a**–**7c** in good to high yields (Entries 1–3). 2-Carboxybenzyl phenyl sulfoxide (**8**) reacted at 80 °C for 8 h to afford 3-phenylthiophthalide (**9**) in 96% yield (Entry 4).

In conclusion, Al-MCM-41 was found to be a useful heterogeneous catalyst for inter- and intramolecular Pummerer reactions of various sulfoxides. The catalytic activity of Al-MCM-41 was superior to that of amorphous silica–alumina or aluminum-free MCM-41 for the reaction of acetic anhydride with **1a**. We assume that the higher catalytic activity of Al-MCM-41 over amorphous silica–alumina is due to the concentration effect of hydrophobic mesopores, which enables a more efficient interaction between the organic substrate and the inner surface of the catalyst.[5d] The catalyst was easily recovered by filtration and could be reused at least three times.

The authors are grateful to Prof. Koichi Narasaka for valuable discussion on this chemistry. Y.K. thanks New Energy and Industrial Technology Development Organization (NEDO) for financial support.

Supporting Information is available on http://dx.doi.org/10.1246/cl.150896.

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7 The specific surface area (BET) and the average pore diameter (BJH) were 1032 $m^2 g^{-1}$ and 2.7 nm, respectively.

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9 In the previous paper, the amount of active sites of Al-MCM-41 (30 mg) was evaluated to be <0.005 mmol by the poisoning experiment using triethylamine.[10] Therefore, the active site of Al-MCM-41 (100 mg) should be <0.017 mmol, and the current reaction is the catalytic reaction.

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11 The use of a stoichiometric amount of Ac_2O (2.0 equiv) in toluene required harsh reaction conditions (100 °C, 17 h) to give the product in good yield (76%).

12 *Typical experimental procedure*: Under an atmosphere of nitrogen, a mixture of Al-MCM-41 (100 mg, dried prior to use with heating gun under vacuum) and ethoxycarbonylmethyl phenyl sulfoxide (**1a**) (0.213 g, 1.0 mmol) in acetic anhydride (5.0 mL) was stirred at 60 °C for 2 h. The catalyst was filtered off and washed with dichloromethane (50 mL). After the combined organic solution was concentrated under reduced pressure, crude product was purified by silica-gel column chromatography (hexane/$Et_2O = 10:1$) to afford ethyl 2-acetoxy-2-(phenylthio)acetate (**2a**) as a colorless oil (0.242 g, 95%). The recovered catalyst was dried at 60 °C for 15 min. The catalyst (75 mg) was then dried with heating gun under vacuum and used in a second run. **2a**: IR (neat): ν_{max} 2981, 1748, 1474, 1441, 1371, 1325, 1258, 1209, 1042, 950, 910, 748, 692 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.57–7.52 (m, 2H), 7.38–7.31 (m, 3H), 6.19 (s, 1H), 4.13 (q, $J = 7.3$ Hz, 2H), 2.19 (s, 3H), 1.19 (t, $J = 7.3$ Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 169.6, 165.8, 134.1, 129.9, 129.1, 129.0, 76.6, 62.0, 20.7, 13.9. HRMS (ESI) found: 255.0691, calcd for $C_{12}H_{15}O_4S$ $[M + H]^+$ 255.0691.