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PII: DOI: Reference:	S0040-4039(14)01161-7 http://dx.doi.org/10.1016/j.tetlet.2014.07.020 TETL 44863
To appear in:	Tetrahedron Letters
Received Date:	26 May 2014
Revised Date:	26 June 2014
Accepted Date:	4 July 2014



Please cite this article as: Ito, S., Kubota, Y., Asami, M., 1,3-Addition of silyl enol ethers to nitrones catalyzed by mesoporous aluminosilicate, *Tetrahedron Letters* (2014), doi: http://dx.doi.org/10.1016/j.tetlet.2014.07.020

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1,3-Addition of silyl enol ethers to nitrones catalyzed by mesoporous aluminosilicate

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Abstract— Mesoporous aluminosilicate (Al-MCM-41) was found to be an effective and reusable catalyst for 1,3-addition of silyl enol ethers to nitrones. The reaction proceeded under mild reaction conditions to afford the corresponding β -(siloxyamino)ketones in high yields. Furthermore, a unique chemoselectivity of a nitrone over an aldehyde and an acetal, which are more reactive toward silyl enol ether in the presence of Al-MCM-41 than a nitrone, was observed.

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Keywords: Al-MCM-41; Solid acid catalyst; 1,3-Addition of nitrones; Chemoselective reaction

Nitrones are generally used for 1,3-dipolar cycloaddition with dipolarophiles to afford the corresponding heterocyclic compounds because of the synthetic utility of the cycloadducts.^{1,2} The reactions of nitrones with silyl enol ethers derived from ketones are known to give the corresponding cycloadducts under heating conditions^{2a} or in the presence of trimethylsilyl trifluoromethanesulfonate (TMSOTf) (Scheme 1a).^{2b} In contrast, the reactions of nitrones with silyl enol ethers derived from esters can afford the corresponding 1,3-adducts in the presence or absence of Lewis acids (Scheme 1b).³ 1,3-Adducts of nitrones, hydroxylamine derivatives, are the precursors of amines and imines, which are synthetically useful intermediates.^{3,4}

We have recently reported that the ordered mesoporous aluminosilicate (AI-MCM-41) could catalyze aldol reactions of silyl enol ethers with aldehydes^{5a} and acetals^{5b} in a heterogeneous manner. The high catalytic activity of Al-MCM-41 was attributed to their uniform pore diameter (2.7 nm) and high surface area (1120 m²/g). The catalyst was easily recovered by filtration and reusable without a significant loss of catalytic activity. Herein, we report that the Al-MCM-41 could catalyze 1,3-addition of nitrones with silyl enol ethers derived from a ketone.



Scheme 1. (a) 1,3-Dipolar cycloaddition of nitrone with silyl enol ether, (b) 1,3-Addition of silyl enol ether to nitrone.

In the first place, the reaction of *C*,*N*-diphenylnitrone (**1a**) and 1-phenyl-1-trimethylsiloxyethene (**2a**) was examined using Al-MCM-41 (Si/Al = 26) synthesized according to a known procedure with slight modification.^{6,7} After drying Al-MCM-41 (25 mg) at 120 °C for 1 h under vacuum, **1a** (0.5 mmol) and **2a** (0.6 mmol) in dichloromethane was added to the catalyst, and the mixture was stirred at 0 °C for 1 h. The catalyst was filtered off and washed with dichloromethane. The filtrate was then concentrated under reduced pressure to give the crude product containing the corresponding 1,3-adduct **3a** in quantitative yield (Table 1, entry 1).⁸ The result was in sharp contrast to the reaction of **1a** with **2a** in refluxing xylene,^{2a} where the corresponding cycloadduct was obtained. The reaction was then carried out in the presence of stoichiometric amount of Lewis acids

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(TMSOTf, TiCl₄, SnCl₄, BF₃·OEt₂, or AlCl₃) under the same reaction conditions as entry 1. The reaction of 1a with 2a using TMSOTf gave a complex mixture and neither 1,3adduct 3a nor cycloadduct was obtained (entry 2), though the reaction of C,N-dialkylnitrone with 2ain TMSOTf dichloromethane using afforded the corresponding cycloadduct in good yields.^{2b} The reactions using TiCl₄, SnCl₄, or BF₃·OEt₂ also afforded complex mixtures without the formation of 3a or cycloadduct (entries 3-5). Although the 1,3-adduct 3a was obtained by using AlCl₃, the catalytic activity of AlCl₃ for the 1,3addition was much lower (35% yield, entry 6) than that of Al-MCM-41. When amorphous silica-alumina (SiO₂- Al_2O_3 , $Si/Al = 31)^9$ or aluminum-free MCM- 41^{10} was used in place of Al-MCM-41, the reaction did not proceed and 1a was recovered quantitatively (entries 7 and 8). These results indicate that the presence of both mesoporous structure and aluminum moiety in the catalyst is indispensable to the high catalytic activity of Al-MCM-41 as was observed in the case of the Al-MCM-41-catalyzed aldol reaction.⁵ When the Al-MCM-41-catalyzed reaction was carried out at 30 °C, the reaction was completed in 15 min to give 3a in 96% isolated yield (entry 9). The recovered catalyst could be reused four times without a significant loss of catalytic activity (entry 10).

 Table 1. 1,3-Addition of silyl enol ether 2a to nitrone 1a.¹¹

 Silica catalyst
 Lewis acid

⁻O、+_Ph N	OSiMe ₃ (50 mg/mmol) or (1.0 equiv) Me ₃ S	iO _N ^{Ph} O		
Ph H	Ph CH ₂ Cl ₂ (0.5	i M)	Ph Ph 3a		
1a	2a 0 °C, 1 h				
	(1.2 equiv)				
Entry	Silica catalyst (Si/Al)	Conv. of	Yield of		
	or Lewis acid	$1a(\%)^{a}$	3a $(\%)^{a}$		
1	Al-MCM-41 (26)	>95	>95		
2	TMSOTf	>95	N.D. ^b		
3	TiCl ₄	49	N.D. ^b		
4	SnCl ₄	53	N.D. ^b		
5	$BF_3 \cdot OEt_2$	43	N.D. ^b		
6	AlCl ₃	37	35		
7	$SiO_2-Al_2O_3(31)$	0	N.D. ^b		
8	MCM-41 (∞)	0	N.D. ^b		
9 ^c	Al-MCM-41 (26)	>95	96 ^d		
10 ^{c,e}	Al-MCM-41 (26)	>95	95 ^d		

^a Determined by ¹H NMR analysis of the crude product using nitromethane as an internal standard unless otherwise noted. ^b Not detected, ^c Reaction was performed at 30 ^oC for 15 min. ^d Isolated yield after column chromatography. ^e Recovered catalyst was used. The result of fifth run is shown.

As Al-MCM-41 showed a charasteristic feature in the reaction of nitrone **1a** and silyl enol ether **2a**, the reaction was applied to various nitrones **1** and silyl enol ethers **2** in dichloromethane at 30 °C (Table 2). Among *N*-phenylnitrones, the reactions of electron-poor nitrones **1b** and **1c**, having chloro or nitro group on the aromatic ring, with **2a** were completed in 15 min to afford the corresponding 1,3-adducts in 96% and 87% yields, respectively (entries 1 and 2). Although the reaction of

electron-rich nitrones 1d and 1e, having methyl or methoxy group on the aromatic ring, with 2a were slower than that of electron-poor nitrones, 1,3-adducts were obtained in high yields (entries 3 and 4). 1,3-Addition of 2a to C-2naphthyl-N-phenylnitrone (1f) or N-phenyl-C-transstyrylnitrone (1g) afforded the product in 86% and 83% yields, respectively (entries 5 and 6). N-Benzyl-Cphenylnitrone (1h) was less reactive than 1a and the reaction was completed in 2.5 h to give the 1,3-adduct in 83% yield (entry 7), whereas the reaction of N-benzyl-C-4nitrophenylnitrone (1i) was completed in 0.5 h (86% yield, entry 8). As bulkier silvl ethers are often useful than trimethylsilyl ethers from a synthetic point of view,¹² 1phenyl-1-triethylsiloxyethene (2b) was applied to the reaction with 1a. The corresponding triethylsilyl (TES) ether of the 1,3-adduct was obtained in 96% yield (entry 9). yield decreased However, the when 1-tertbutyldimethylsiloxy-1-phenylethene (2c) was employed (41% yield, entry 10).

Table 2. 1,3-Addition of silyl enol ethers to variousnitrones catalyzed by Al-MCM-41.8

$\overline{O}_{N}^{+}, \mathbb{R}^{2} O_{Si}^{+}$			Al-MCM-41 (50 mg/mmol, Si/Al = 26)			<i>Si</i> O_ _N _R ² O	
B1 F	$B^1 H \to Ph$		CH ₂ Cl ₂ (0.5 M), 30 ℃				
1		2					3
	(1	.2 equiv)					
Enter	1	\mathbb{R}^1		\mathbf{D}^2	2 ^a	Time	Yield
Entry	I			к		(h)	$(\%)^{b}$
1 ^c	b	4-ClC ₆ H ₄		Ph	a	0.25	96
2^{d}	с	$4-NO_2C_6H_4$		Ph	a	0.25	87
3	d	$4 - MeC_6H_4$		Ph	a	1	91
$4^{\rm e}$	e	4-MeOC ₆ H ₄		Ph	a	2	95
5	f	2-Naphtyl		Ph	a	0.25	94
6 ^{c,e}	g	(E)-PhĈH=CH		Ph	a	2	86
$7^{\rm e}$	h	Ph		Bn	a	2.5	83
8^{e}	i	$4 - NO_2C_6H_4$		Bn	a	0.5	86
9	a	Ph		Ph	b	0.25	96
10	a	Ph		Ph	с	5	41
a	0.5	A1 <i>G</i> :		<i>a</i> : <i>a</i>		a hr 1	. 1 . 1 1

^a 2a, $Si = SiMe_3$; 2b, Si = TES; 2c, Si = TBDMS. ^b Isolated yield after column chromatography. ^c CH₂Cl₂ (0.25 M). ^d CH₂Cl₂ (0.1 M). ^e 2a (2.0 equiv) was used.

In the case of Al-MCM-41-catalyzed aldol reaction, Al-MCM-41 promoted the reaction with complete chemoselectivity. That is, only benzaldehyde dimethyl acetal (5) reacted with 2a in the presence of both benzaldehyde (4) and 5.5^b Therefore, the Al-MCM-41catalyzed reaction of 1a (0.5 mmol) and 2a (0.6 mmol) was examined in the presence of 4 (0.5 mmol) in dichloromethane at 30 °C for 15 min. Interestingly, only 1a reacted with 2a to give 3a in quantitative yield,¹⁴ though the aldol reaction of 2a with 4 was much faster than the 1,3-addition of **2a** to **1a**.^{5a,13} Moreover, **1a** was selectively reacted with 2a also in the presence of 5 to afford 3a in 88% vield under the same reaction conditions (Table 3). The origin of the reversed reactivity was considered to be in the high adsorption ability of the nitrone for the acid sites of Al-MCM-41. The hypothesis was further supported

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by the result that electron-rich nitrone 1d, which should have higher adsorption ability than electron-poor nitrone 1b, was preferentially reacted with 2a in the presence of 1b (Scheme 2). Namely, the reaction of 2a with 1b and 1d in dichloromethane at 30 °C for 1 h gave 3d in 71% yield and 3b was obtained in 19% yield although the reactivity of 1b in the absence of 1d was higher than that of 1d in the absence of 1b (Table 2, entries 1 and 3).

 Table 3. Chemoselective 1,3-addition of nitrone 1a over aldehyde 4 and acetal 5.



^a Determined by ¹H NMR analysis of the crude product using nitromethane as an internal standard. Yields are based on the corresponding substrates. ^b Not detected.



Scheme 2. Chemoselective 1,3-addition of nitrone 1d over nitrone 1b.

In summary, 1,3-addition reaction of silyl enol ethers to various nitrones was achieved by using Al-MCM-41 as a reusable solid acid catalyst. The corresponding β -(siloxyamino)ketones were obtained in high yields under mild reaction conditions. Moreover, Al-MCM-41 was found to effect interesting chemoselectivive activations because of the selective adsorption of the substrates on the catalyst.

Acknowledgments

Y.K. thanks New Energy and Industrial Technology Development Organization (NEDO) for financial support.

Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.201X.XX.XXX.

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- 7. The specific surface area (BET) and the average pore diameter (BJH) were $1120\ m^2/g$ and 2.7 nm, respectively.
- 8. The structure of the 1,3-adducts was fully characterized by IR and $^1\text{H},\,^{13}\text{C}$ NMR spectroscopy.
- 9. Amorphous silica–alumina (SiO₂–Al₂O₃, Si/Al = 31) was synthesized according to the same procedure as the one used in the synthesis of Al-MCM-41 without the addition of surfactant, cethyltrimethylammonium bromide. The specific surface area (BET) was 385 m²/g.
- 10. Aluminum-free MCM-41 was synthesized according to the same procedure as the one used in the synthesis of Al-MCM-41 without the addition of aluminum source, Al(OⁱPr)₃. The specific surface area (BET) and the average pore diameter (BJH) were 1080 m²/g and 2.6 nm, respectively.
- 11. Typical experimental procedure for Al-MCM-41-catalyzed 1,3-addition of silyl enol ethers to nitrones (Table 1, entry 8): Under an atmosphere of argon, to a mixture of C,N-diphenylnitrone (1a) (98.6 mg, 0.50 mmol) and Al-MCM-41 (25 mg, Si/Al = 26, dried prior to use at 120 °C for 1 h under vacuum) in dichloromethane (0.5 mL), 1-phenyl-1-trimethylsiloxyethene (2a) (115 mg, 0.60 mmol) in dichloromethane (0.5 mL) was added through a syringe at 30 °C. The reaction mixture was stirred at 30 °C for 15 min. The catalyst was removed by filtration and washed with dichloromethane (40 mL). The filtrate was concentrated under reduced pressure, and nitromethane (30.5 mg, 0.50 mmol) in

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CDCl₃ (1.0 mL) was then added to the crude product as an internal standard. After the crude product was analyzed by ¹H NMR spectroscopy, nitromethane and CDCl₃ were removed under reduced pressure. The residue was purified by silica-gel column chromatography (hexane/Et₂O=15:1) to give 3-[phenyl(trimethylsiloxy)amino]-1,3-diphenylpropan-1-one (3a) as a colorless oil (187 mg, 96%); IR (neat): ν_{max} 2958, 1686, 1597, 1487, 1449, 1251, 878, 844, 751, 697 cm⁻¹; ¹H NMR (270 MHz, CDCl₃): δ (ppm) 7.88 (d, J = 7.6 Hz, 2H), 6.96–7.56 (m, 13H), 5.11 (dd, J = 8.4, 5.0 Hz, 1H), 3.75 (dd, J = 17.3, 8.4 Hz, 1H), 3.58 (dd, J = 17.3, 5.0 Hz, 1H), -0.14 (s, 9H); ¹³C NMR (67.8 MHz, CDCl₃): δ (ppm) 197.6, 152.1, 138.6, 136.9, 132.7, 129.3, 128.3, 128.0, 127.8, 127.7, 127.4, 123.3, 120.1, 69.4, 37.5, -0.6.

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- 13. The reaction of 4 with 2a (1.2 equiv) in acetonitrile at 0 °C was completed in 15 min to give the corresponding aldol adduct in 99% yield.^{5a} On the other hand, the reaction of 1awith 2a (1.2 equiv) in dichloromethane at 0 °C required 1 h to give 3a in quantitative yield (Table 1, entry 1).

14. Excess 2a was recovered as acetophenone.

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