Journal of the Korean Chemical Society 2007, Vol. 51, No. 4 Printed in the Republic of Korea

NaHSO₄·SiO₂촉매를 이용한 Knoevenagel 축합을 거친 α,β의 불포화산, α-Cyanoacrylonitriles와 α-Cyanoacrylates의 합성을 위한 무수조건하의 반응 절차

M. Gopalakrishnan*, P. Sureshkumar, V. Kanagarajan, J. Thanusu, and S. Thirunavukkarasu Department of Chemistry, Annamalai University, Annamalai Nagar-608 002 (2007. 4. 3 접수)

Dry Media Reaction Procedure for Synthesis of α,β-Unsaturated Acids, α-Cyanoacrylonitriles and α-Cyanoacrylates *via* Knoevenagel Condensation Using NaHSO₄·SiO₂ Catalyst

M. Gopalakrishnan*, P. Sureshkumar, V. Kanagarajan, J. Thanusu, and S. Thirunavukkarasu Department of Chemistry, Annamalai University, Annamalai Nagar-608 002 (Received April 3, 2007)

요 약. NaHSO₄ SiO₂를 사용하는 solvent-free 조건하에서 E-geometry를 가진 α,β의 불포화산, α-Cyanoacrylonitriles 와 α-Cyanoacrylates의 효율적인 입체선택적 반응을 수행하였다.

주제어: NaHSO₄·SiO₂, Knoevenagel축합, Arylidene 화합물, Solvent-free solid-state 반응, (E)-3-(2-butyl-4-chloro-1*H*-imidazol-5-yl)acrylic acid; Microwave irradiation

ABSTRACT. Efficient stereoselective synthesis of α , β -Unsaturated acids, α -Cyanoacrylonitriles and α -Cyanoacrylates has been carried out in the presence of NaHSO₄.SiO₂ under solvent–free conditions with an *E*-geometry. **Keywords:** Silica Gel Supported Sodium Hydrogen Sulphate, Knoevenagel Condensation, Arylidene Compounds, Solvent-free Solid-state Reactions, (*E*)-3-(2-butyl-4-chloro-1*H*-imidazol-5-yl)acrylic Acid, Microwave Irradiation

INTRODUCTION

One of the more important properties of Knoevenagel condensation from a synthetic perspective is that they offer a route to the formation of C-C bond, by which the arylidene compounds are obtained from carbonyl compounds and active methylene compounds in the presence of a basic catalyst or Lewis acid catalyst.¹ In recent times, there has been a growing interest in Knoevenagel products because many of them have significant biological activity, for example, tyrophostins, such as α -cyanothiocinnamide, are known to inhibit autophosphorylation of the EGF receptor, in addition to possessing antiproliferative effects on human keratinocytes.² Knoevenagel condensation reaction has been widely used in organic synthesis to prepare coumarins and their derivatives, which are important intermediates in the synthesis of cosmetics, perfumes and pharmaceuticals.³ The first procedure for this condensation reaction was reported by Knoevenagel⁴ more than a century ago. This has led to the development of several new synthetic strategies involving weak bases⁵ and few acid catalysts.⁶ More recently, ionic liquids⁷ have also been employed to accomplish this reaction. Also, Knoevenagel reaction was enhanced by microwave irradiation.⁸ However, all these methods have their own merits and shortcomings. Since Knoevenagel condensation is a versatile reaction in medical and organic chemistry, development of an alternative synthetic methodology is of paramount importance.

Solvent- free solid state synthetic methods have been shown to be very efficient and advantageously coupled with microwave (MW) activation9 and many organic reactions have been carried out using "microwave induced organic reaction enhancement" (MORE) technique delivering high yields in a short reaction time compared with the conventional heating mode performed in preheated thermostat oil bath.¹⁰ The use of supported reagents has attracted much attention because of the selectivity, reactivity and associated ease of manipulation.¹¹ Microwave induced chemical reactions¹² especially on solid supports and those conducted in solvent less systems,13 have gained popularity. While planning to select a suitable mild acid for catalyzing the condensation reaction, we thought that a catalyst known for activation of an electrophile should serve the purpose.

Silica gel supported sodium hydrogen sulfate (NaHSO₄·SiO₂)¹⁴ a non-toxic and inexpensive catalyst, has been used for a number of organic reactions including one-pot conversion of ketones to amides,¹⁵ and single step synthesis of 4(3H)-quinazolinones.¹⁶

RESULTS AND DISCUSSION

Solvent- free Solid-State organic reactions using dry media techniques under microwave irradiation are a main topic of interest in our laboratory.^{17,18,19} In continuation of these efforts aimed at developing solvent- free procedures we found that the use of silica gel supported sodium hydrogen sulfate (NaHSO₄·SiO₂) catalyzed nucleophilic attack on the carbonyl group by various active methylene compounds like malonic acid, malononitrile, ethyl cyanoacetate and served as a dehydrating agent to facilitate the removal of water in the final step both under microwave irradiation and thermal conditions. NaHSO₄·SiO₂ heterogeneous catalyst reacts with structurally diverse aromatic aldehydes and various active methylene compounds (*Scheme* 1) under mild condition to



Scheme 1. Solid-state Knoevenagel condensation of aromatic aldehydes with active methylene compounds catalyzed by $NaHSO_4$ ·SiO₂.

give the corresponding arylidene compounds in quantitative yields (*Table* 1) without any of the environmental disadvantages of using toxic and costly drying reagents such as zirconophosphate oxynitride.^{Sd} NaHSO₄·SiO₂ catalyst was shown to be one of the most efficient MW absorber with a very high specificity to MW heating. It was able to reach a temperature of 110 °C after 3 minutes of irradiation in a domestic oven (320 W).

The reaction has been carried out at different power levels from 80-720 W (*Table* 1, entries 3, 12 & 19) in order to select the more appropriate power level and found out that power level of 320 W gave the maximum yield.

The reaction is highly stereoselective, results in the formation of arylidene compounds in excellent yields, with an E - geometry. Both electron-rich and electron-deficient aldehydes worked well, affording good to excellent yields of products. Moreover, treatment of heterocyclic aldehyde like furfural with various active methylene compounds resulted in the formation of the corresponding arylidene products in good yield.

Moreover, in order to check the possibility of specific non- thermal effects of microwave irradiation, reactions were carried out using thermostated heating mantle (Δ) under similar sets of conditions of time and temperature as for the microwave-assisted method (*Table 2*).

Significant lower yields were obtained under conventional heating than using MW- assisted method under identical conditions of time and temperature. Even by extending reaction times, yields remain lower under thermal conditions when compared to MW activation. This observation clearly demonstrates that the effect of MW irradiation is

Table 1. NaHSO₄·SiO₂ catalyzed condensation of aromatic aldehydes with active methylene compounds in solvent-free conditions under microwave irradiation

Entm	Ar	Х	Y	Reaction conditions		Isolated yields	m.p. (°C)
Entry				Temperaturea (°C)	Time ^b (s)	(%)	Found / Reported
1	C ₆ H ₅	COOH	COOH	54-56	70	96	131-32/133
2	2-CH ₃ OC ₆ H ₅ -	COOH	COOH	68-70	94	81	182-83/185-86
3	$4-CH_3OC_6H_5-$	COOH	COOH	67-70	90	87	168-69/170
4	$4-CH_3C_6H_5-$	COOH	COOH	52-54	90	82	195/198-99
5	$3-FC_6H_5-$	COOH	COOH	67-69	95	88	163/165
6	2-ClC ₆ H ₅ -	COOH	COOH	63-65	95	85	210-11/212
7	3-ClC ₆ H ₅ -	COOH	COOH	64-66	92	82	174/176
8	4-ClC ₆ H ₅ -	COOH	COOH	65-67	85	89	241-43/245
9	$3-NO_2C_6H_5$ -	COOH	COOH	67-69	95	79	198-99/200-01
10	$4-NO_2C_6H_5$	COOH	COOH	55-57	90	83	282-84/286
11	C ₆ H ₅ -	CN	CN	54-57	75	92	81/82
12	4-CH ₃ OC ₆ H ₅ -	CN	CN	58-60	80	95	115/116-17
13	$4-CH_3C_6H_5-$	CN	CN	60-62	85	93	125-26/128-30
14	4-OHC ₆ H₅-	CN	CN	54-56	95	86	185-86/188
15	4-ClC ₆ H ₅ -	CN	CN	58-60	85	90	160/161
16	$4-NO_2C_6H_5-$	CN	CN	60-62	85	92	157-58/159
17	Furfural	CN	CN	60-62	90	85	73/72
18	C ₆ H ₅ -	CN	COOEt	55-57	85	94	48/49
19	$4-CH_3OC_6H_5$	CN	COOEt	60-62	85	94	88/90
20	$4-CH_3C_6H_5$	CN	COOEt	58-60	88	92	89/91-92
21	$4-OHC_6H_5$	CN	COOEt	56-58	96	88	170-71/172
22	$4-ClC_6H_5$	CN	COOEt	64-66	90	91	88-89/90
23	$4-NO_2C_6H_5$	CN	COOEt	67-69	90	93	165-66/168
24	Furfural	CN	COOEt	58-60	95	89	91-92/93

^aFinal temperature was measured by immersing a glass thermometer in the reaction mixture at the end of the exposure to microwave irradiation and gives an approximate temperature range.

^bTime at which maximum yield was obtained.

^cIsolated yields of pure products; all products were characterized by IR, ¹H NMR and MS spectra.

not purely thermal.

A credible reaction pathway for the product formation is depicted in *Scheme* 2.

Another noteworthy feature of NaHSO₄.SiO₂ catalyst lies in the fact that it can be recovered and reused by simple washing with diethyl ether after each use and activated in an oven at 120 °C for 1 h prior to use, rendering thus the process more economic and green. In total, eight successive re-use runs were possible. However, little palpable decrease in the reaction yield was noted up to five runs (*Table* 1, entries 3, 12 & 19). All these constitute a green and efficient alternative to the MW assisted method described by Kim *et al.*⁵ using piperidine and chlorobenzene.

In addition, by applying the above synthetic procedure, (*E*)-3-(2-butyl-4-chloro-1*H*-imidazol-5-yl)acrylic acid, a model compound is synthesized by condensing 2-butyl-4-chloro-1*H*-imidazol-5-carbaldehyde with malonic acid in the presence of NaHSO₄·SiO₂ catalyst under microwave irradiation at a power level of 320 W for 90 sec/ thermal condition at 60 °C for 540 sec. The reaction mixture was cooled and extracted with dichloromethane (3×10 mL). The catalyst was removed by filteration. After drying the dichloromethane extracts over anhydrous Na₂SO₄ the combined organic phases were concentrated *in vacuo* to furnish the product.

ation and Classical thermal conditions (Power – 320 w)							
Entry	Method	T (°C)	Time (s)	Yield (%)			
	MW	54-56	70	96			
1	Δ	55	70	34			
	Δ	55	420	88			
	MW	67-70	90	87			
3	Δ	60	90	24			
	Δ	60	540	81			
	MW	55-57	90	83			
10	Δ	55	90	20			
	Δ	55	660	75			
	MW	58-60	80	95			
12	Δ	60	80	33			
	Δ	60	600	82			
	MW	60-62	85	94			
19	Δ	65	85	18			
	Δ	65	780	84			
	MW	56-58	96	88			
21	Δ	60	96	25			
	Δ	60	960	80			
	MW	58-60	95	89			
24	Δ	65	95	32			
	Δ	65	900	81			

Table 2. Comparison of results under both Microwave Irradiation and Classical thermal conditions (Power = 320 W)

EXPERIMENTAL

General remarks

All the inorganic and organic chemicals were purchased from commercial suppliers and were used without purification prior to use. The reactions were monitored by TLC to ascertain proof of reactions. Melting points were recorded in open capillaries (uncorrected). The FT-IR spectra were recorded on a NICOLET AVATAR-360 FT-IR spectrophotometer. ¹H NMR spectra were recorded on a BRUKER AMX–400 NMR spectrometer (400 MHz) in CDCl₃ using TMS as internal standard. Mass spectra were recorded in FINNIGAN MAT–8230 MASS spectrometer operating at 70 eV. Satisfactory microanalysis was obtained on Carlo Erba 1106 CHN analyzer. A conventional (unmodified) household microwave oven equipped with a turntable (LG MG–395 WA, 760 W and operating at 2450 MHz) was used for the microwave irradiation experiments. NaHSO₄·SiO₂ catalyst was prepared according to the literature.¹⁶

General procedure for the synthesis of 4-methoxycinnamic acid (*Table* 1, entry 3)

To a mixture of 4-methoxybenzaldehyde (1.36 g, 10 mmol) and NaHSO₄·SiO₂ catalyst (50 mg) in a 50 mL borosil beaker, malonic acid (1.04g, 10 mmol) was added. The reaction mixture was mixed properly with the help of a glass rod (10 s) and then irradiated in a domestic microwave oven for 90 s at a power level of 320 W (monitored by TLC). The reaction mixture was cooled and extracted with Et₂O (3×10 mL). The catalyst was removed by filteration and reused. After drying the ether extracts over anhydrous Na₂SO₄ the combined organic phases were concentrated *in vacuo* to furnish the product



Scheme 2. Credible reaction pathway for product formation.



Scheme 3. Dry media synthesis of (E)-3-(2-butyl-4-chloro-1H-imidazol-5-yl)acrylic acid.

(1.54 g, 87%).

The reaction was also performed with 4-methoxybenzaldehyde (6.80 g, 50 mmol), NaHSO₄·SiO₂ catalyst (250 mg) and malonic acid (5.20 g, 50 mmol) in a 150 mL borosil beaker adopting the same procedure. After an irradiation time of 90 s, the product (7.61 g, 86%) was obtained. The structure of the compounds was confirmed by FT–IR, ¹H NMR, MS and comparison with authentic samples obtained commercially or prepared by reported methods.

(*E*)-3-(2-butyl-4-chloro-1*H*-imidazol-5-yl)acrylic acid **26**: m.p. 160-62°C, IR, cm⁻¹: 3462, 3331, 3028, 2973, 2933, 2857, 2805, 2643, 2542, 1683, 1553; ¹H NMR δ ppm: 0.94 (t, 3H, H₁₂, J=6.2 Hz), 1.31-35 (m, 2H, H₁₁), 1.60-1.64 (m, 2H, H₁₀), 2.54 (t, 2H, H₉, J=6.3 Hz), 6.48 (d, 1H, H₇, J=15.9 Hz), 7.82 (d, 1H, H₆, J=16.2 Hz), 11.90 (s, 1H, H₈), 11.99 (s, 1H, H₁); ESI MS: 229 (M+1)⁺; Carbon: 52.48_{found} (52.52_{cal}), Hydrogen: 5.69_{found} (5.73_{cal}); Nitrogen: 12.21_{found} (12.25_{cal}).

CONCLUSION

Crisply, this article describes a novel and efficient approach for the rapid synthesis of various arylidene compounds by the condensation of aromatic aldehydes with active methylene compounds under microwave irradiation in solvent- free conditions using re-usable NaHSO₄·SiO₂ as an inexpensive and environmentally benign catalytic system. The notable features of this procedure are mild reaction conditions, operational simplicity, improved yields and enhanced reaction rates, cleaner reaction profiles and simple experimental and product separation procedures making this method an attractive one.

REFERENCES

- 1. Jones, G. Org. React. 1967, 15, 204.
- a) Lyall, R.; Zilberstein, A.; Gazit, A.; Gilonj, C.; Levitzki, A.; Schlessinger, J. J. Biol. Chem. 1989, 264, 14503-14509. b) Shiraishi, T.; Owada, M.K.; Tatsuki, M.; Yamashita, Y.; Kaunaga, T. Cancer Res. 1989, 49, 2374-2378.
- a) Tietze, L.F.; Beifuss, U. In comprehensive Organic Synthesis (Eds.: Trost, B.M.; Fleming, I.; Heathcock, C.K.); Pergamon Press: Oxford, **1991**, vol. 2, pp. 341-392. b) Bigi, F.; Chesini, L.; Maggi, R.; Sartori, G. J. Org. Chem. **1999**, 64, 1033-1035. c) Yu, N.; Aramini, M.; Germann, M.W.; Huang, Z. Tetrahedron Lett. **2000**, 41, 6993-6996.
- 4. Knoevenagel, E. Berichte, 1898, 31, 2585-2596.
- 5. a) Allen, C.F.H.; Spangler, F.W. Org. Synth. Coll. Vol. III, 1955, 377-379. b) Rand, L.; Swisher, J.V.; Cronin, C.J. J. Org. Chem. 1962, 27, 3505-3507. c) Cardillo, G.; Fabbroni, S.; Gentilucci, L.; Gianotti, M.; Tolomelli, A. Synth. Commun. 2003, 33, 1587-1594. d) Fripiat, N.; Grange, P. Chem. Commun. (Cambridge), 1997, 1781. e) Kim, J.; Kwon, P.; Kwon, T.; Chung, S.; Lee, J. Synth. Commun. 1996, 26, 535.
- 6. a) Rao, P.S.; Venkataratnam, R.V. *Tetrahedron Lett.* **1991**, *32*, 5821-5822. b) Prajapati, D.; Lekhok, K. C.; Sandhu, J. S.; Ghosh, A. C. *J.Chem. Soc. Perkin Trans. 1*, **1996**, 959-960.
- 7. a) Su, C.; Chen, Z.-C.; Zheng, Q.G. Synthesis, 2003, 555-559. b) Harjani, J.R.; Nara, S.J.; Salunkhe, M.M. *Tetrahedron Lett.* 2002, 43, 1127-1130.
- a) Balalaie, S.; Nemati, N. Synth. Commun. 2000, 30, 869. b) Dave, C.G; Augustine, C. Indian J Chem. 2000, 39B, 403.
- a) Loupy, A.; Petit, A.; Hamelin, J.; Texier-Boullet, F.; Jacquault, P.; Mathe, D. *Synthesis*, **1998**, 1213. b) Varma, R.S. *Green Chem.* **1999**, *1*, 43.
- 10. a) Caddick, S. Tetrahedron, 1995, 51, 10403. b) Langa,

Journal of the Korean Chemical Society

NaHSO, SiO,촉매를 이용한 Knoevenagel 축합을 거친 α,β의 불포화산, α-Cyanoacrylonitriles와 α-Cyanoacrylates의 합성 351

F.; De la Cruz, P.; De la Hoz, A.; Diez-Barra, E. Contemp. Org. Synth. **1997**, 373.

- 11. a) McKillop, A.; Young, D. W. Synthesis, 1979, 401 and 481. b) Balogh, M.; Laszlo, P. Organic Chemistry Using Clays, Springer Verlag, Berlin, 1993. c) Clark, J. H. Catalysis of Organic Reactions by Supported Organic Reagents, VCH Publishers Inc.; New York, 1994.
- Yadav, J. S.; Reddy, B. V. S.; Satheesh, G.; Lakshimi, P. N.; Kunvar, A. C. *Tetrahedron Lett.* 2003, 45, 8587.
- Rodriguez, H.; Suarez, M.; Perez, R.; Petit, A.; Loupy, A. *Tetrahedron Lett.* **2003**, *44*, 3709.

- 14. Brewton, G. W. J. Org. Chem. 1997, 62, 8952.
- Das, B.; Ravindranath, N.; Venkataiah, Madhusudan, P. J. Chem. Res. (S), 2000, 482.
- 16. Das, B.; Banerjee, J. Chem. Lett. 2004, 8, 960.
- Gopalakrishnan, M.; Sureshkumar, P.; Kanagarajan, V; Thanusu, J.; Govindaraju, R. J. Chem. Res. 2005, 5, 299.
- Gopalakrishnan, M.; Sureshkumar, P.; Kanagarajan, V.; Thanusu, J. Lett. Org. Chem. 2005, 2, 444.
- Gopalakrishnan, M.; Sureshkumar, P.; Kanagarajan, V.; Thanusu, J. Catalysis Communications, 2005, 6, 753.