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Highly Efficient Formylation of Alcohols, Thiols and Aniline Derivatives by a Heterogeneous ($HCOOH/SiO_2$) System under Microwave Irradiation and Solvent-free Conditions

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ABSTRACT

A simple, rapid and efficient microwave-assisted procedure for the formylation of aniline derivatives and alcohols, using a heterogeneous ($HCOOH/SiO_2$) system under solvent-free conditions is reported. The method is applied to a set of amines, alcohols and thiols and short reaction times (<10 min) with high yields are reported. This protocol introduces a practical and viable green technology of solvent-free and catalyst-free reactions.

KEYWORDS

Alcohols, anilines, SiO_2, HCOOH, microwave irradiation, solvent-free conditions.

1. Introduction

Microwave-promoted chemical reactions are energy efficient, since irradiation for only a few minutes is adequate for conducting most endothermic reactions. For exothermic reactions, it is necessary to provide only a short burst of energy to initiate the reaction. After this initiation, the reaction proceeds to completion without the need for any additional energy from an external source. Formylation of alcohols and amines is an important transformation in organic synthesis and provides an efficient method for the protection of OH and NH groups. *N*-formyl compounds have been widely used in organic synthesis as a protecting group. Thus a number of formylating methods have been reported. Acetic formic anhydride[1–3] is one of the most widely used formylating agents. However, because of its sensitivity to atmospheric moisture it is easily decomposed to acetic acid and carbon monoxide. Other useful formylating agents include chloral,[4] activated formic acid using DCC,[5] or EDCI,[6] activated formic esters,[7–10] ammonium formate[11] and formic acid itself under reflux conditions.[12–14]

A variety of catalysts have been used for activating these reagents, such as $Sc(OTf)_3$ and $Sc(NTf_2)_3$,[15] $TiCl(OTf)_3$,[16] TMSCl and TMSOTf,[17] $La(i\text{-}Pr)_3$,[18] $COCl_2$,[19] $Sn(OTf)_2$,[20] $TiCl_4$ and $AgClO_4$,[21] $AlPW_{12}O_{40}$,[22] PCl_3-$n(SiO_2)_n$,[23] PPh_3/CBr_4,[24] $K_5CoW_{12}O_{40}.3H_2O$[25] and CCl_3CHO/K_2CO_3.[26] Some of the reagents reported for formylation are often hazardous, toxic, expensive, not readily available and need to be freshly prepared, the reactions require drastic conditions or prolonged reaction times and tedious work-up procedures are involved. Thus, milder, non-hazardous and inexpensive reagents are still in demand.

2. Results and Discussion

Keeping in view our general interest in the development of friendlier synthetic procedures, a rapid, high-yielding preparation of *N*-formyl and *O*-formyl compounds was attempted. We wish to report results of a method utilizing microwave irradiation in the presence of a silica gel/formic acid heterogeneous system in which the solid silica support may be recycled after product separation (Scheme 1).

To explore the generality and scope of this reaction a wide range of structurally different alcohols, aniline derivatives and thiols was subjected to formylation under these conditions. The results are shown in Table 1. It is clear that we were able to develop a convenient and efficient procedure for the formylation of aniline (entries 1–6), amino acid (entry 7) and macrocyclic amine (entry 8) derivatives. The reaction showed good results for a wide variety of structurally different starting materials. Reactions of aniline bearing both electron-donating and electron-withdrawing groups proceeded smoothly to give the corresponding *N*-formyl compounds in quantitative yields.

In a similar manner, various substituted aromatic and aliphatic hydroxyl groups were smoothly formylated under mild reaction conditions and gave the desired *O*-formylated alcohols in high yields. These procedures are uniformly effective for the formylation of primary and secondary saturated alcohols (Table 1, entries 19–27), benzylic alcohols (Table 1, entries 9–15), phenols (Table 1, entries 17 and 18) and cholesterol (Table 1, entry 28).

Our experiments also indicated that tertiary alcohols (Table 1, entry 29) and thiols (Table 1, entries 30–32) were not formylated under these conditions. Also, the results show that this method is selective for the formylation of aniline and alcohols in the presence of phenols (Scheme 2).

The advantages of $HCOOH/SiO_2$ over reported reagents in the

X: **N**, **O**, **S**
R: alkyl, aryl
R': alkyl, aryl, H

Scheme 1

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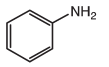
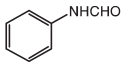
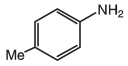
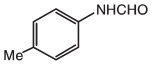
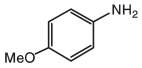
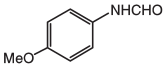
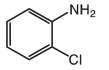
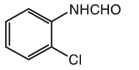
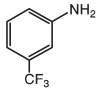
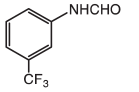
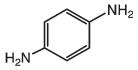
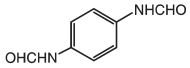
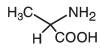
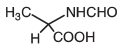
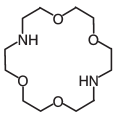
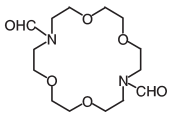
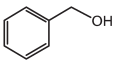
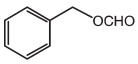
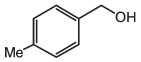
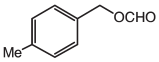
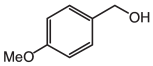
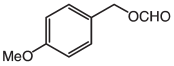
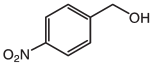
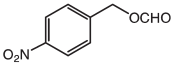
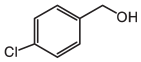
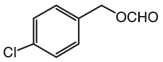
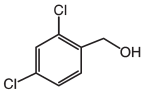
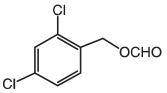
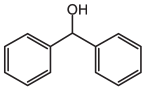
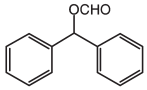
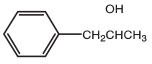
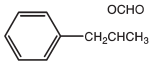
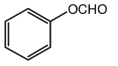
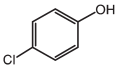
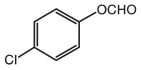
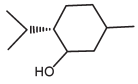
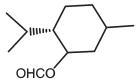
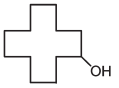
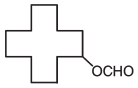
Table 1 Formylation of alcohols and amines utilizing a heterogeneous ($HCOOH/SiO_2$) system under microwave irradiation.

Entry	Substrate	Product	Time/min	Yield/% [a]	Ref.
1			3	99	28
2			1	98	33
3			2	98	28
4			2.5	96	28
5			2	96	–
6			3.5	95	–
7			4	92	32
8			5	98	–
9			2	95	23
10			1	99	29
11			1	100	23
12			3	95	30
13			1.5	96	23
14			1	95	–
15			2	96	30
16			3	92	27
17			10	55	31
18			10	50	–
19			4	96	27
20			4.5	94	26
21			3	90	25
22			5	96	27
23			3.5	90	25

Continued on p. 41

Table 1 (*continued*)

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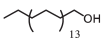
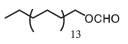
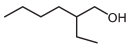
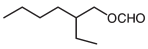
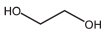
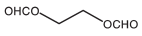
24			4	87	24
25			5	75	27
26			10	96	29
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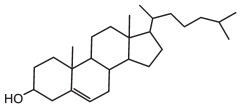
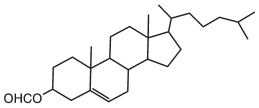
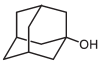
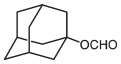
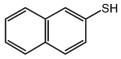
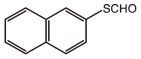
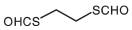
28			6	98	23
29			10	0	–
30			10	0	–
31			10	0	–
32			10	0	–

[a] Products were characterized from their physical properties, comparison with authentic samples and by spectroscopic methods.

formylation of benzyl alcohol, menthol and aniline, are shown in Table 2. These results show that our method is milder than the other methods.

In conclusion, it was demonstrated that combining SiO_2 with microwave energy is an efficient, fast, convenient and easy workup procedure for the synthesis of *N*-formyl and *O*-formyl compounds. The present method has additional advantages such as mild conditions, chemoselectivity, good to high yields, non-corrosive and inexpensive reagents, recycling of the catalyst and environmentally friendly conditions. Moreover, this protocol introduces a practical and viable green technology of solvent-free and catalyst-free reactions.

3. Experimental

IR and NMR spectra were recorded using a Shimadzu 435-U04 spectrophotometer (Kyoto, Japan) (KBr pellets) and a Jeol 90 MHz FT-NMR spectrometer (Tokyo, Japan), respectively.

3.1. Preparation of $HCOOH/SiO_2$

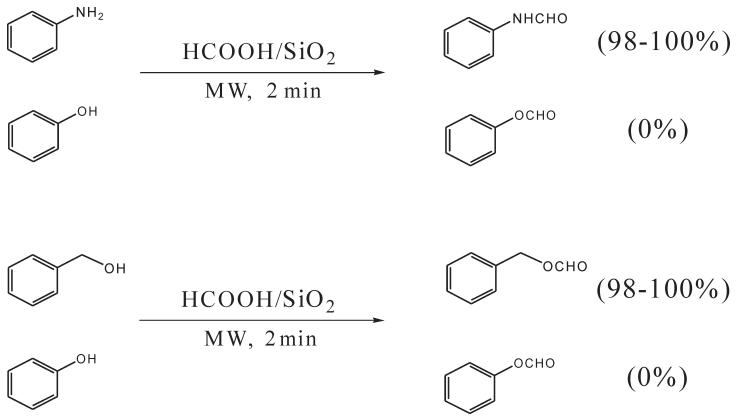
Formic acid (1 mL) was added to 1 g of silica gel (mesh 70–230) with stirring for 1 min at room temperature.

3.2. General Procedure for Formylation of Alcohols, Thiols and Aniline Derivatives using TBBDA and PBBS under Microwave Irradiation and Solvent-free Conditions

Alcohol (or amine) (1 mmol) and the above mixture were added to a round-bottomed flask (25 mL). The flask was placed in a bath containing SiO_2 to enable absorption of additional microwave irradiation. The flask was irradiated in a microwave oven (LG Co., Seoul, Korea) 230 V, ~50 Hz, RF output 900 W) at a power output of 900 W at 110 °C for a certain period of time. The progress of each reaction was monitored by TLC using n-hexane:acetone (4:1) as the solvent. After completion of the reaction the obtained mixture was allowed to cool, eluted with ethanol and filtered to remove the silica gel. Evaporation of the solvent under reduced pressure gave the pure product in excellent yield.

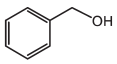
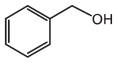
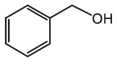
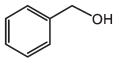
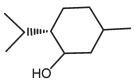
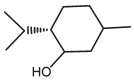
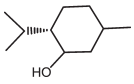
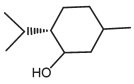
Analytical data for unknown compounds:

Compound (5): IR (KBr): 3210, 2950, 1685, 1600, 1458, 1370, 1250, 1140, 1120 and 1040 cm^{-1}; ^1H NMR ($CDCl_3$, 250 MHz): δ 6.5–7.8 (m, CH aromatic, 4H), 7.8 (b, NH, 1H) and 8.56 ppm (s, CHO, 1H). Anal. calcd for $C_8H_6F_3NO$: C, 50.80; H, 3.20; N, 7.41; found: C, 50.62; H, 3.12; N, 7.28. m/z: 189.



Scheme 2

Table 2 Comparison of reaction times and yields using our reagents relative to previously published methods.

Entry	Substrate	Catalysts	Time/min	Yield/%	Ref.
1		$HCOOH/SiO_2$	2	95	–
2		$TiCl_3(OTf)$	240	83	30
3		$K_5CoW_{12}O_{40}.3H_2O$	60	90	25
4		PCl_3-n$(SiO_2)_n$	20	95	23
5		$HCOOH/SiO_2$	4	96	–
6		$TiCl_3(OTf)$	720	90	30
7		$K_5CoW_{12}O_{40}.3H_2O$	60	81	25
8		PCl_3-n$(SiO_2)_n$	60	94	23
9		HCOOH/SiO2	3	99	–
10		TiCl3(OTf)	720	91	30
11		PCl3-n$(SiO_2)_n$	75	92	23

Compound (6): IR (KBr): 3293, 2980, 1690, 1603, 1450, 1377, 1250, 1159 and 1011 cm^{-1}; ^1H NMR ($CDCl_3$, 250 MHz): δ 6.8–7.8 (dd, CH aromatic, 4H), 7.9 (b, NH, 2H) and 8.50 ppm (s, CHO, 2H). Anal. calcd for $C_8H_8N_2O_2$: C, 58.53; H, 4.91; N, 17.06; found: C, 58.26; H, 4.63; N, 16.85. m/z: 164.

Compound (8): IR (KBr): 1668, 1463, 1378, 1320, 1211, 1121 and 1001 cm^{-1}; ^1H NMR ($CDCl_3$, 250 MHz): δ 3.46 (s, CH_2, 24H) and 7.92 ppm (s, CHO, 2H). Anal. calcd. for $C_{14}H_{26}N_2O_6$: C, 52.82; H, 8.23; N, 8.80; found: C, 52.89; H, 7.85; N, 8.65. m/z: 318.

Compound (14): IR (KBr): 3094, 2927, 2855, 1730, 1592, 1564, 1475, 1365, 1242, 1161, 1104 and 1004 cm^{-1}; ^1H NMR ($CDCl_3$, 250 MHz): δ 5.22 (s, CH_2, 2H), 7.28–8.35 (m, CH aromatic, 3H) and 8.11 ppm (s, CHO, 1H). Anal. calcd for $C_8H_6Cl_2O_2$: C, 46.86; H, 2.95; N, 34.58; found: C, 46.18; H, 2.65; N, 15.06. m/z: 205.

Compound (18): IR (KBr): 3070, 3023, 2845, 1724, 1600, 1565, 1487, 1456, 1153 and 1054 cm^{-1}; ^1H NMR ($CDCl_3$, 250 MHz): δ 7.52 (dd, CH aromatic, 4H) and 8.30 ppm (s, CHO, 1H). Anal. calcd. for $C_7H_5ClO_2$: C, 53.70; H, 3.22; found: C, 53.46; H, 2.98. m/z: 156.

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References

1 J.C. Sheehan and D.D.H. Yang, *J. Am. Chem. Soc.*, 1958, **80**, 1154–1158.
2 T.W. Green and P.G.M. Wuts, *Protective Groups in Organic Synthesis,* 3rd edn., Wiley-Interscience, New York, NY, USA,1999.
3 P. Strazzolini, A.G. Giumanini and S. Cauci, *Tetrahedron,* 1990, **46**, 1081–1118.
4 F.F. Blicke and C.J. Lu, *J. Am. Chem. Soc.*, 1952, **74**, 3933–3934.
5 J. Waki and J. Meienhofer, *J. Org. Chem.*, 1977, **42**, 2019–2020.
6 F.M.F. Chen and N.L. Benoiton, *Synthesis,* 1979, 709–713.
7 H.L. Yale, *J. Org. Chem.* , 1971, **36**, 3238–3240.
8 L. Kisfaludy and O. Laszlo, *Synthesis,* 1987, 510–513.
9 M. Neveux, C. Bruneau and P.H. Dixneuf, *J. Chem. Soc., Perkin Trans.*, 1991, 1197–1199.
10 W. Duczek, J. Deutsch, S. Vieth and H. J. Niclas, *Synthesis,* 1996, 37–38.
11 P.G. Reddy, G.D.K. Kumar and S. Baskaran, *Tetrahedron Lett.*, 2000, **41**, 9149–9151.
12 S. Treppendhal and P. Jakobsen, *Acta Chem. Scand., Ser. B,* 1978, **32**, 697–700.
13 S.H. Jung, J.H. Ahn, S.K. Park and J.K. Choi, *Bull. Korean Chem. Soc.*, 2002, **23**,149–152.
14 A. Khoramabadi-Zad, H. Veisi, S.A. Akbari and A. Shiri, *J. Chin. Chem. Soc.*, 2007, **54**, 479–481.
15 K. Ishihara, M. Kubota and H. Yamamoto, *Synlett,* 1996, 265–268.
16 J. Izumi, I. Shiina and T. Mukaiyama, *Chem. Lett.*, 1995, 141–145.
17 R. Kumareswaran, A. Gupta and Y.D. Vankar, *Synth. Commun.*, 1997, **27**, 227–282.
18 T. Okano, K. Miyamoto and K. Kiji, *Chem. Lett.*, 1995, 246–249.
19 J. Iqbal and R.R. Srivastava, *J. Org. Chem.*, 1992, **57**, 2001–2004.
20 T. Mukaiyama, I. Shiina and M. Miyashita, *Chem. Lett.*, 1992, 625–629.
21 M. Miyashita, I. Shiina and T. Mukaiyama, *Bull. Chem. Soc. Jpn.*, 1993, **66**, 1516–1518.
22 H. Firouzabadi, N. Iranpoor, F. Nowrouzi and K. Amani, *Chem. Commun.*, 2003, 764–769.

23 N. Iranpoor, H. Firouzabadi and A. Jamalian, *Tetrahedron Lett.,* 2005, **46**, 7963–7966.

24 H. Hagiwara, K. Morohashi, H. Sakai, T. Suzuki and M. Ando, *Tetrahedron,* 1998, **54**, 5845–5852.

25 M. Habibi, S. Tangestaninejad, V. Mirkhani and B. Yadollahi, *Tetrahedron,* 2001, **57**, 8333–8337.

26 R.N. Ram and N.K. Meher, *Tetrahedron,* 2002, **58**, 2997–3001.

27 F. Shirini, K. Marjani, H.T. Nahzomi and M.A. Zolfigol, *Phosphorus,. Sulfur and Silicon,* 2007, **182**, 1245–1251.

28 B. Das, M. Krishnaiah, P. Balasubramanyam, B. Veeranjaneyulu and D.N. Kumar, *Tetrahedron Lett.,* 2008, **49**, 2225–2227.

29 H.J. Park and J.C. Lee, *Bull. Korean Chem. Soc.* 2008, **29**, 856–858.

30 H. Firouzabadi, N. Iranpoor and S. Farahi, *J. Mol. Catal. A: Chem.,* 2008, **289**, 61–68.

31 P. Strazzolini, A. G. Giumanini and S. Cauci, *Tetrahedron,* 1990, **46**, 1081–1118.

32 P. Chandra, S. Hausmann and A. Metz, *Pharm. Res. Commun.,* 1974, **6**, 311–317.

33 T.V. Pratap and S. Baskaran, *Tetrahedron Lett.,* 2001, **42**, 1983–1985.