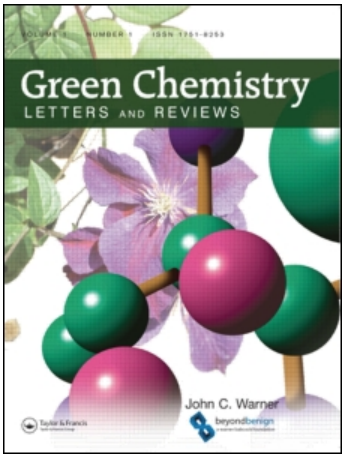


Green Chemistry Letters and Reviews
Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t748292817

Uncatalyzed synthesis of thiomorpholide using polyethylene glycol as green reaction media

Shrikant S. Gawande[a]; Babasaheb P. Bandgar[b]; Prasad D. Kadam[b]; Shailesh S. Sable[c]
[a] Organic Chemistry Research Laboratory, School of Chemical Sciences, Swami Ramanand Teerth Marathwada University, Vishnupuri, Nanded, India [b] Organic Chemistry Research Laboratory, School of Chemical Sciences, Solapur University, Solapur, India [c] National Chemical Laboratory, Chemical Engineering and Process Development Division, Pune, India

Online publication date: 08 December 2010

To cite this Article Gawande, Shrikant S. , Bandgar, Babasaheb P. , Kadam, Prasad D. and Sable, Shailesh S.(2010) 'Uncatalyzed synthesis of thiomorpholide using polyethylene glycol as green reaction media', Green Chemistry Letters and Reviews, 3: 4, 315 — 318
To link to this Article: DOI: 10.1080/17518253.2010.486772
URL: http://dx.doi.org/10.1080/17518253.2010.486772

Green Chemistry Letters and Reviews
Vol. 3, No. 4, December 2010, 315–318

Taylor & Francis
Taylor & Francis Group

RESEARCH LETTER

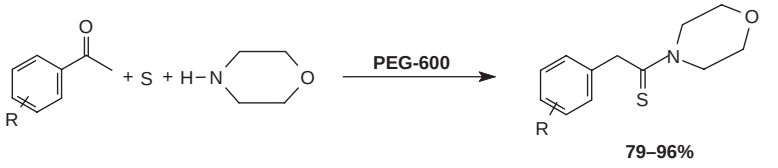
Uncatalyzed synthesis of thiomorpholide using polyethylene glycol as green reaction media

Shrikant S. Gawande[a], Babasaheb P. Bandgar[b]*, Prasad D. Kadam[b] and Shailesh S. Sable[c]

[a]*Organic Chemistry Research Laboratory, School of Chemical Sciences, Swami Ramanand Teerth Marathwada University, Vishnupuri, Nanded 431606, India;* [b]*Organic Chemistry Research Laboratory, School of Chemical Sciences, Solapur University, Solapur 413255, India;* [c]*National Chemical Laboratory, Chemical Engineering and Process Development Division, Dr. Homi Bhabha Road, Pune 411008, India*

(Received 13 August 2009; final version received 12 April 2010)

Polyethylene glycol-600 was used as an efficient and recyclable solvent for the one-pot three component condensation reactions of aryl alkyl ketones, sulfur, and morpholine to produce the corresponding thiomorpholide. This protocol has advantages of high yields, short reaction times, mild reaction conditions, minimal environmental pollution, and simple work up procedure.



Keywords: thiomorpholide; polyethylene glycol-600; sulfur; Willgerodt–Kindler reaction

Introduction

Thioamides are of importance in medicinal chemistry (*1*) due to their biological activity, against bacterial infection (*2*), as fungicides (*3*), herbicides (*4*), and activators of *L*-asparaginase (*5*). Apart from these applications, Thioamides are known to be versatile intermediates in organic synthesis (*6*). Particularly in the field of peptide chemistry (*7*), as well as building blocks for the synthesis of five and six membered heterocycles (*8–11*). A traditional approach to their synthesis is the Willgerodt–Kindler reaction which has found only limited application because of the high reaction temperatures and long reaction periods required and the low to moderate yields obtained (*12–14*).The synthesis of thiomorpholide has also been carried out using microwave (*15,16*), but this method requires special reaction instruments and conditions. In recent years, though ionic liquids (ILs) have been found to be effective solvents to improve the Willgerodt–Kindler reaction with good result (*17*), the limitation of the use of ILs as solvents is that the cost is usually expensive and they are difficult to use on an industrial scale (*18*).

Green chemistry is one of the important focuses within organic synthesis, thus it attracts more scientists and researchers to this area. Polyethylene glycol (PEG), which is considered a benign medium due to low vapor pressure, non-flammability, the ease of work up, the ability to act as phase transfer catalysts, good reaction medium, inexpensive price, and eco-friendly for nature (*19–22*), seems to be a perfect solvent alternative to volatile organic solvents and ILs. In fact, PEG has had universal uses in organic reactions for a long time (*23,24*). Various kinds of research have been reported that use PEG as the solvent or medium for organic chemistry (*25–28*). As a part of our on-going research program directed toward the development of new and rapid synthetic methods for the construction of biologically active structural motifs, we intended to develop a rapid, efficient, economic, and easy to scale-up method for the synthesis of thiomorpholide using PEG-600 as green reaction media (Scheme 1).

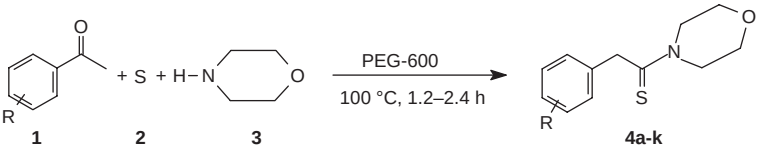
Results and discussion

In the initial studies, the reaction of acetophenone (2 mmol), sulfur (2 mmol), and morpholine (2 mmol)

*Corresponding author. Email: bandgar_bp@yahoo.com

ISSN 1751-8253 print/ISSN 1751-7192 online

DOI: 10.1080/17518253.2010.486772
http://www.informaworld.com



Scheme 1. Synthesis of thiomorpholide using PEG-600 as green reaction media.

was performed in different solvents without any added catalyst to synthesize the compound 1-Morpholin-4-yl-2-phenyl-ethanethione (**4a**). It was observed that among the tested solvents (Table 1, Entries 4–7), the reaction (Table 1, Entry 4) in PEG-600 was more facile and proceeded to give best yields (96%) when the reaction mixture was stirred at 100°C for 1.2 hours. Moreover, there are many potential advantages of replacing these volatile or toxic organic solvents with PEG-600. Therefore, PEG-600 is an optimal reaction medium for the reaction.

The effect of temperature was also been studied by carrying out the model reaction of 1-Morpholin-4-yl-2-phenyl-ethanethione (**4a**) in PEG-600 at different temperatures. As shown in Table 1 (Entries 1–2), the reaction did proceed when the reaction temperature was 35°C or 50°C. However, the obtained yield remained low even after longer reaction time (24 h). However, at elevated temperature (75–100°C) using PEG-600 gave better results in terms of yield and reaction time. Hence, the conditions of Entry 4, shown in Table 1, were the optimized reaction conditions.

In order to evaluate the generality of the process, we studied the reaction of various aryl alkyl ketones with morpholine and sulfur in PEG-600 at 100°C. The results are presented in Table 2. Both electron rich as well as electron deficient acetophenones reacted well with morpholine in the presence of sulfur to give thioamides in excellent yields. Bulky and sterically hindered substrates such as 2-hydroxyacetophenone, 2-acetylnaphthalene, and 2-aminoacetophenone reacted smoothly under similar conditions to produce the corresponding thioamides (Table 2, Entries g, i, and j). In the case of halogenated acetophenones, no side products were observed arising from nucleophilic displacement of halogen by morpholine under these conditions (Table 2, Entry b).

Table 1. Synthesis of thiomorpholide using PEG-600 as green reaction media.

Entry	Solvent	Temperature (°C)	Time (h)	Yield[a] (%)
1	PEG-600	35	24	2
2	PEG-600	50	24	10
3	PEG-600	75	5	78
4	PEG-600	100	1.2	96
5	PEG-600	110	1.2	96
6	Methanol	63	5	32
7	Ethanol	75	5	40

[a]Isolated yields.

In the present procedure, PEG-600 acts as a clean solvent. Moreover, PEG-600 is a recyclable reagent. In the reaction of 1-Morpholin-4-yl-2-phenyl-ethanethione (**4a**) (Figure 1), we recycled PEG-600 three times and the reaction proceeded cleanly with good yields, 91%, 88%, and 82% (Figure 1, Run 1, 2, and 3), respectively. Slight weight loss of PEG-600 was observed from cycle to cycle due to mechanical loss. The present methodology offers very attractive features such as excellent yields, simple reaction conditions, and easy work up. Moreover, the use of PEG-600 as reaction medium makes this process a green synthesis.

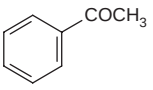
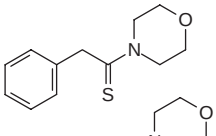
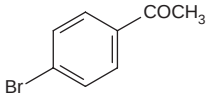
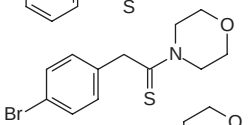
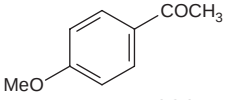
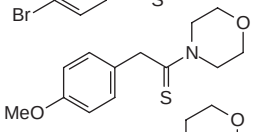
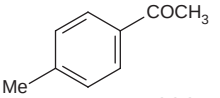
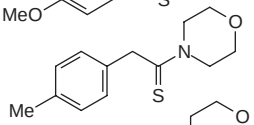
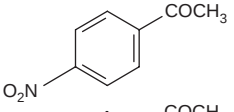
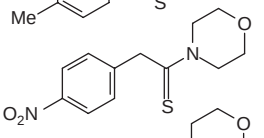
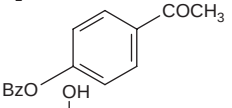
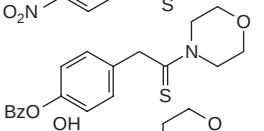
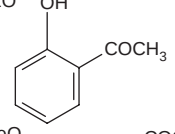
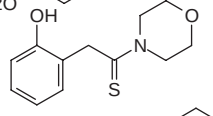
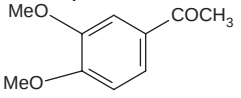
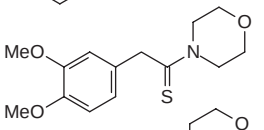
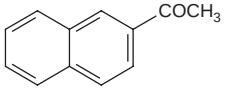
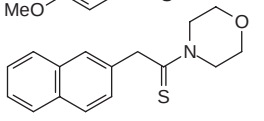
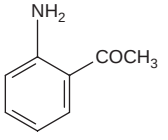
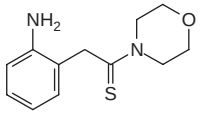
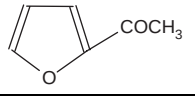
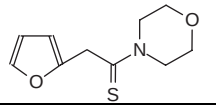
In the classical Willgerodt–Kindler reaction, morpholine was generally used in large excess as a solvent, as well as a reactant (*12,15*). The use of PEG-600 as a solvent minimizes the quantity of morpholine in the reaction. This is because of the activation of ketones by PEG-600. The main advantage of this procedure is that high conversions (79–96%) were achieved in short reaction times (1.2–2.4 h) by using PEG-600.

Experimental

General remarks

All chemicals were purchased from Sigma–Aldrich and Lancaster and were used as such. All reactions and purity of thiomorpholide compounds (**4a–k**) were monitored by thin layer chromatography (TLC) using aluminum plates coated with silica gel (Merck) using 20% ethyl acetate and 80% hexane as eluent. IR spectra were recorded on Perkin–Elmer FTIR-1710 spectrophotometer using Nujol film. ^{1}H NMR spectra were recorded on a Bruker Avance Spectrospin 300 (300 MHz) using TMS as internal standard and chemical shift are in $\triangle$. GC–MS mass spectra were recorded on a Waters LCT Micromass. The temperature of the reaction mixture was measured through a non-contact infrared thermometer (AZ, Mini Gun type, Model 8868).

Table 2. Synthesis of thiomorpholide using PEG-600 as green reaction media.

Entry	Substrate (1)	Product[a] (4)	Isolated yield (%)	Time (h)
a			96	1.2
b			93	1.3
c			89	1.5
d			85	1.4
e			79	2.4
f			92	1.8
g			91	1.2
h			88	2.0
i			83	1.6
j			93	1.3
k			87	1.9

[a]Structural assignments of the products are based on their ^{1}H NMR, ^{13}C NMR, IR, and MS spectral data (*14–16*).

General procedure for the synthesis of thiomorpholide

In a 50 ml round bottom flask, acetophenone (2 mmol), sulfur (2 mmol), and morpholine (2 mmol) in PEG-600 (1 ml) were mixed and stirred at 100°C for an appropriate time (Table 2), then treated with cool water. The solid product (**4a**), which separated out, was filtered, washed with water and dried. The crude product was recrystallized from ethanol. The progress of the reaction was monitored by TLC using hexane-ethyl acetate (8:2). In the recycled reaction, after isolation of the product from the reaction system, the mother liquor, which is the mixture of PEG-600 and water, extracted with ether (PEG being insoluble in ether). The ether layer was decanted, and mother liquor dried for 4 h under the infrared light or distilled directly to eliminate water. The next run was performed using the same conditions.

Selected physical and spectral data

*1-Morpholin-4-yl-2-phenyl-ethanethione (**4a**)*. Yellow solid, m.p.: 60–65°C, IR (KBr): υ_{max}: 3474, 3023, 2966, 2860, 1964, 1710, 1485, 1274, 1104, 958, 705, and 624 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): $\triangle$ 7.17–7.22 (m, 5H), 4.30–4.35 (t, 2H), 4.30 (s, 2H), 3.70–3.78 (t, 2H), 3.55–3.52 (t, 2H), and 3.30–3.40 (t, 2H); ES-MS E/Z 221 (M^+).

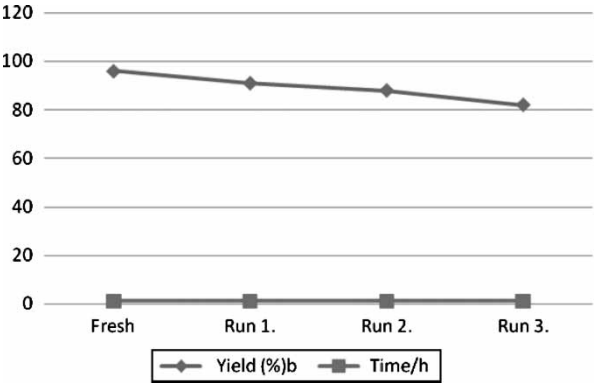


Figure 1. Recycling yields.
[a]Reaction condition: acetophenone (2 mmol), sulfur (2 mmol), and morpholine (2 mmol); solvent PEG-600; 100°C.
[b]Isolated and unoptimized yields.

2-(4-Bromo-phenyl)-1-morpholin-4-yl-ethanethione (***4b***). Light yellow solid, m.p.: 92–96°C, IR (KBr): υ_{max}: 3414, 2921, 2857, 1485, 1434, 1271, 1217, 1110, 1032, 960, 724, and 612 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): Δ 7.40–7.50 (d, $J = 7.49$ Hz, 2H), 7.20 (d, $J = 6.50$ Hz, 2H), 4.35 (t, 2H), 4.22 (s, 2H), 3.70–3.80 (t, 2H), 3.60 (t, 2H), and 3.40 (t, 2H); ES-MS E/Z 300 (M^+).

Conclusion

In summary, we report a novel, mild, and highly efficient protocol for the three-component condensation of aryl alkyl ketones, sulfur, and morpholine to produce thiomorpholides in PEG-600. The present method has some notable advantages compared to the previous methods such as high conversions, operational simplicity, enhanced reaction rates, cleaner reaction profiles, and ease of isolation of products, which makes the process potentially useful for industrial applications for the synthesis of thiomorpholides. We indicated that PEG-600 can replace traditional organic solvents and some ILs in the reaction. PEG-600 is a favorable solvent which sets a good example of green chemistry.

Acknowledgements

The authors are thankful to The Director, School of Chemical Sciences, Swami Ramanand Teerth Marathwada University, Vishnupuri, Nanded for providing laboratory facilities.

References

(1) Smith, J.; Liras, J.L.; Schneider, S.E.; Anslyn, E.V. *J. Org. Chem.* **1996**, *61*, 8811–8818.
(2) Mallams, A.K.; Morton, J.B.; Reichert, P.J. *J. Chem. Soc. Perkin Trans.* **1981**, *1*, 2186–2208.
(3) Schroeder, D.C. *Chem. Rev.* **1955**, *55*, 181–228.
(4) Sarkis, G.Y.; Faisal, E.D. *J. Heterocycl. Chem.* **1985**, *22*, 137–140.
(5) Bandgar, B.P.; Gawande, S.S.; Warangkar, S.C.; Totre, J.V. *Bioorg. Med. Chem.* **2010**, *18*, 3618–3624.
(6) Metzner, P. *Synthesis* **1992,** *12*, 1185–1199.
(7) Weinstein, B., Ed., *Chemistry and Biochemistry of Amino Acids, Peptides and Proteins*: *a survey of recent developments*, Marcel Dekker Inc., New York, 1983; Vol. 7, pp. 267–357.
(8) Jagodzinski, S.T. *Chem. Rev.* **2003**, *103*, 197–227.
(9) Griffin, T.S.; Woods, T.S.; Klayman, D.L. In *Advances in Heterocyclic Chemistry;* Katritzky, A.R., Boulton, A.J., Eds.; Academic Press: New York, 1975; Vol. 18, pp 99.
(10) Moghaddam, F.M.; Boinee, H.Z. *Tetrahed. Lett.* **2003**, *44,* 6253–6255.
(11) Moghaddam, F.M.; Boinee, H.Z. *Tetrahedron* **2004**, *60*, 6085–6089.
(12) Brown, E.V. *Synthesis* **1975,** 358–373, and references cited therein.
(13) Sheldon, R. *J. Chem. Soc. Chem. Commun.* **2001**, 2399–2407.
(14) Gordon, C.M. *Appl. Catal. A: Gen.* **2001**, *222*, 101–117.
(15) Nooshabadi, M.; Aghapoor, K.; Darabi, H.R.; Mojtahedi, M.M. *Tetrahed. Lett.* **1999**, *44*, 7549–7552.
(16) Moghaddam, F.M.; Hojabri, L.; Dohendou, M. *Synth. Commun.* ***2003****, 24*, 4279–4284.
(17) Yadav, J.S.; Reddy, B.V.S.; Kondaji, G.; Reddy, J.S.S.; Nagaiah, K. *J. Mol. Catal. A: Chem.* **2007**, *266*, 249–253.
(18) Laus, G.; Bentivoglio, G.; Schottenberger, H.; Kahlenberg, V.; Kopacka, H.; Röder, T.; Sixta, H. *Lenzinger Berichte* ***2005****, 84,* 71–85.
(19) Harris, J.M.; Hundley, N.H.; Shannon, T.G.; Evelyn, C. *J. Org. Chem.* **1982**, *47*, 4789–4791.
(20) Baj, S.; Siewniak, A. *Appl. Catal. A: Gen.* **2007**, *321*, 175–179.
(21) Heldebrant, D.J.; Jessop, P.G. *J. Am. Chem. Soc.* **2003**, *125*, 5600–5601.
(22) Chen, J.; Spear, S.K.; Huddleston, J.G.; Rogers, R.D. *Green Chem.* **2005**, *7*, 64–82.
(23) Kleber, C.; Andrade, Z.; Alves, L.M. *Curr. Org. Chem.* **2005**, *9,* 195–218.
(24) Feng, B.; Hu, Y.; Li, H.; Hou, Z.S. *Chin. J. Org. Chem.* **2008**, *28*, 381–389.
(25) Kidwai, M.; Bhatnagar, D.; Mishra, N.K.; Bansal, V. *Catal. Commun.* ***2008****, 9*, 2547–2549.
(26) Bandgar, B.P.; Patil, S.A.; Korbad, B.L.; Bandgar, S.B.; Hote, B.S. *Aust. J. Chem.* ***2008****, 61* (7), 552–555.
(27) Bandgar, B.P.; Patil, S.A.; Korbad, B.L.; Bandgar, S.B.; Hote, B.S.; Chavan, V. *Aust. J. Chem.* ***2008****, 61* (9), 700–703.
(28) Das, B.; Krishnaiah, M.; Balasubramanyam, P.; Veeranjaneyulu, B.; Kumar, D.N. *Tetrahed. Lett.* ***2008****, 49*, 2225–2227.