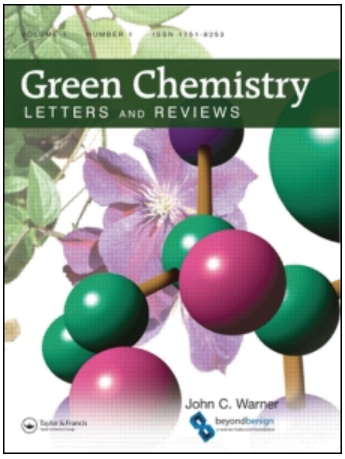

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Bhaskar S. Dawane[a]; Baseer M. Shaikh[a]; Namdev T. Khandare[a]; Vinod T. Kamble[b]; Santosh S. Chobe[a]; Shankaraiah G. Konda[a]
[a] Organic Research Laboratory, Department of Chemistry, Yeshwant Mahavidyalaya, Nanded, Maharashtra, India [b] Organic Research Laboratory, School of Chemical Sciences, Swami Ramanand Teerth Marathwada University, Nanded, Maharashtra, India

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RESEARCH LETTER

Eco-friendly polyethylene glycol-400: a rapid and efficient recyclable reaction medium for the synthesis of thiazole derivatives

Bhaskar S. Dawane[a]*, Baseer M. Shaikh[a], Namdev T. Khandare[a], Vinod T. Kamble[b], Santosh S. Chobe[a] and Shankaraiah G. Konda[a]

[a]*Organic Research Laboratory, Department of Chemistry, Yeshwant Mahavidyalaya, Nanded 431602, Maharashtra, India;* [b]*Organic Research Laboratory, School of Chemical Sciences, Swami Ramanand Teerth Marathwada University, Nanded 431606, Maharashtra, India*

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An efficient and convenient procedure for the synthesis of thiazole derivatives from α-haloketone, thiourea and substituted acetophenones using polyethylene glycol-400 as a green and recyclable solvent is described. Significant rate enhancement and improved yields have been observed.

Keywords: polyethylene glycol; α-haloketones; thiourea; substituted acetophenones; thiazole derivatives

Introduction

The thiazole ring system is an important class of compounds in medicinal chemistry. This structure has applications in drug development for the treatment of allergies (*1*), hypertension (*2*), inflammation (*3*), cardiotonic (*4*), fungicidal (*5*), schizophrenia (*6*), HIV infection (*7*), mental retardation in children, age-related and neurodegenerative brain damage (Alzheimer's disease, Parkinson's disease), and others (*8–10*). Despite their importance from a pharmacological and synthetic point of view, comparatively few methods for their preparation have been reported in the literature. The Hantzsch thiazoles synthesis (*11*) involves the condensation of α-haloketones with thioureas or thioamides under drastic conditions. The main drawbacks of this method are low yields and long reaction times. The modified methods of King and Dadson (*12–14*), as well as those of other research groups (*15*), have also been reported for the synthesis of thiazole derivatives. However, these methods suffer from one or more disadvantages, such as harsh reaction conditions, unsatisfactory yields, cumbersome product isolation procedures, and the use of volatile organic solvents. Therefore, the development of improved methods for the synthesis of thiazole derivatives has acquired relevance to current research.

Recently, liquid polymers or low melting polymers have emerged as alternative green reaction media with unique properties, such as thermal stability, commercial availability, non-volatility, immiscibility with a number of organic solvents, and recyclability (*16–18*). Polyethylene glycol (PEG) solvent is preferred over other polymers because they are inexpensive, completely non-halogenated, easily degradable, and of low toxicity (*19*).

Results and discussion

In view of the recent emphasis toward the development of new, selective, and environmental friendly methodologies using PEG-400 as a solvent for the synthesis of fine chemicals and biologically important compounds, herein we report an efficient method for the synthesis of thiazole derivatives by one-pot condensation of α-haloketone, thiourea, and substituted acetophenones using PEG-400 (Scheme 1).

Initially we investigated the reaction of α-haloketone, thiourea, and 2-hydroxy-5-chloro acetophenone in PEG-400 at 40°C to afford the corresponding product (**4e**) in 92% yield. In order to optimize the reaction conditions, we carried out the above reaction in different solvents, such as ethanol, dichloromethane, acetonitrile, isopropyl alcohol, benzene, and PEG-400 (Table 1). We found PEG-400 an efficient reaction medium in terms of reaction time as well as yield (92%). This result encouraged us to carry out the reaction on several acetophenones in PEG-400 at 40°C to afford the corresponding products in excellent yields (Table 2). In addition, the recylclabilty of the PEG-400 was

*Corresponding author: bhaskardawane@rediffmail.com

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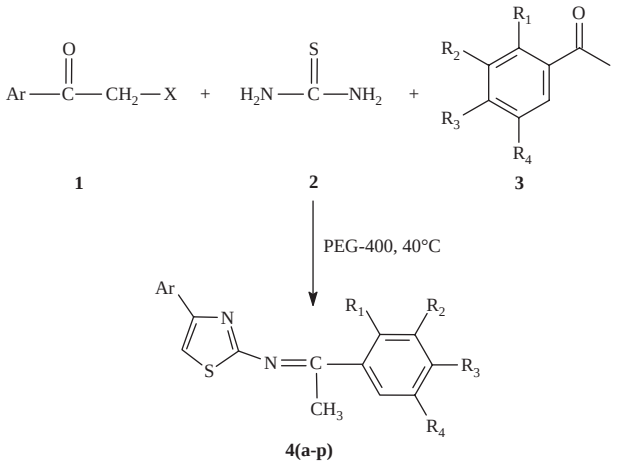

Scheme 1. Synthesis of a thiazole derivative.

Table 1. Solvent effect on the reaction of α-haloketone, thiourea, and 2-hydroxy-5-chloro-acetophenone at 40°C.

Entry	Solvent	Time (min)	Yield (%)
1	EtOH	40	80
2	DCM	45	75
3	CH_3CN	35	82
4	IPA	40	84
5	C_6H_6	50	60
6	PEG-400	18	92

investigated and revealed the important observation that the PEG-400 was recovered and reused for five runs without loss of its activity (Table 3).

When attempts were made to carry out the reaction of α-haloketone, thiourea, and 2-hydroxy-5-chloro acetophenone by reported methods (*15*), the yield of the corresponding product was poor (50%). In general, reactions in PEG-400 are clean, rapid, and afford higher yields than those obtained by the above mentioned method.

Experimental

Melting points were uncorrected and determined in open capillary tubes. The purity of the products was checked by thin layer chromatography (TLC) on precoated sheets of silica gel-G of 0.25 mm thickness. IR spectra were recorded (in KBr palates) on FTIR Schimadju spectrometer. ^{1}H NMR spectra were recorded in DMSO-d_6 in Avance 300 MHz spectrometer using TMS as an internal standard. The mass spectra were recorded on Ei-Schimadju-GC-MS mass spectrometer. Elemental analyses were performed on a Carlo Erba 106 Perkin-Elmer model 240 analyzer.

Typical one-pot procedure for the synthesis of thiazole derivatives

A mixture of 2-hydroxy-5-chloro-α-haloketone (5 mmol), thiourea (5 mmol), and 2-hydroxy-5-chloro-acetophenone (5 mmol) were stirred at around 40°C in PEG-400 (10 ml) for an appropriate time (Table 2). The progress of the reaction was monitored by TLC. After completion of the reaction, the mixture was extracted with ethyl acetate (2×10 ml). The combined organic layer was dried over anhydrous Na_2SO_4 and the solvent was evaporated under reduced pressure. The crude product was recrystallized with aqueous acetic acid to afford the pure product in 92% yield.

Table 2. Synthesis of thiazolyl-imino phenols using PEG-400 as solvent.

Product	X	R_1	R_2	R_3	R_4	Ar	Time (min)	Yield (%)	MP (°C)
4a	Br	OH	H	H	Cl	4-Cl-C_6H_5	20	92	150
4b	Br	OH	H	H	H	4-Cl-C_6H_5	18	91	160
4c	Br	OH	Cl	H	Cl	4-Cl-C_6H_5	25	95	102
4d	Br	OH	I	H	Cl	4-Cl-C_6H_5	28	90	180
4e	Cl	OH	H	H	Cl	2-OH-5-Cl-C_6H_4	18	92	141
4f	Cl	OH	H	H	H	2-OH-5-Cl-C_6H_4	15	90	125
4g	Cl	OH	Cl	H	Cl	2-OH-5-Cl-C_6H_4	20	94	169
4h	Cl	OH	I	H	Cl	2-OH-5-Cl-C_6H_4	22	92	175
4i	Cl	OH	H	H	Cl	2-OH-3-Iodo-5-Cl-C_6H_3	19	93	152
4j	Cl	OH	H	H	H	2-OH-3-Iodo-5-Cl-C_6H_3	15	94	138
4k	Cl	OH	Cl	H	Cl	2-OH-3-Iodo-5-Cl-C_6H_3	24	91	170
4l	Cl	OH	I	H	Cl	2-OH-3-Iodo-5-Cl-C_6H_3	27	89	165
4m	Br	OH	H	H	Cl	4-NO_2-C_6H_5	17	90	172
4n	Br	OH	H	H	H	4-NO_2-C_6H_5	20	93	118
4o	Br	OH	Cl	H	Cl	4-NO_2-C_6H_5	25	91	156
4p	Br	OH	I	H	Cl	4-NO_2-C_6H_5	29	88	147

Table 3. Recycling of PEG-400 for the reaction of α-haloketone, thiourea, and 2-hydroxy-5-chloro-acetophenone.

Entry	Run	Time (min)	Yield (%)
1	First	18	92
2	Second	20	90
3	Third	20	90
4	Fourth	21	89
5	Fifth	21	88

Spectroscopic data of selected compounds

4a: Brown crystal; IR (KBr): 3200 (−OH), 1633 (−C=N) cm^{-1}; ^1H NMR (DMSO-d_6): δ = 2.50 (s, 3H, CH_3), 7.10 (s, 1H, 5H of thiazole), 7.48–7.80 (m, 6H, Ar–H), 10.91 (s, 1H, OH, D_2O exchangeable); ^{13}C NMR: δ = 17.7, 112, 119, 127, 128 (2C), 129 (2C), 130, 131, 133, 134, 152, 160, 164, 172; EIMS: m/z = 363 [M^+]; Anal. Calcd. for $C_{17}H_{12}ON_2SCl_2$: C, 56.43; H, 3.29; N, 7.68%. Found: C, 51.35; H, 3.25; N, 7.35%.

4b: Yellow crystal; IR (KBr): 3280 (−OH), 1630 (−C=N) cm^{-1}; ^1H NMR (DMSO-d_6): δ = 2.50 (s, 3H, CH_3), 7.10 (s, 1H, 5H of thiazole), 7.48–7.80 (m, 6H, Ar–H), 10.22 (s, 1H, OH, D_2O exchangeable); EIMS: m/z = 328 [M^+]; Anal. Calcd. for $C_{17}H_{13}ON_2SCl$: C, 62.19; H, 3.96; N, 8.54%. Found: C, 61.15; H, 3.65; N, 8.12%.

4c: Yellow fine crystal; IR (KBr): 3292 (−OH), 1618 (−C=N) cm^{-1}; ^1H NMR (DMSO-d_6): δ = 2.70 (s, 3H, CH_3), 7.13 (s, 1H, 5H of thiazole), 7.48–8.16 (m, 6H, Ar–H), 12.91 (s, 1H, OH, D_2O exchangeable); EIMS: m/z = 397 [M^+]; Anal. Calcd. for $C_{17}H_{11}ON_2SCl_3$: C, 51.35; H, 2.70; N, 7.04%. Found: C, 51.48; H, 2.58; N, 7.16%.

4d: Dark red; IR (KBr): 3267 (−OH), 1621 (−C=N) cm^{-1}; ^1H NMR (DMSO-d_6): δ = 2.60 (s, 3H, CH_3), 7.15 (s, 1H, 5H of thiazole), 7.42–8.05 (m, 6H, Ar–H), 12.54 (s, 1H, OH, D_2O exchangeable); EIMS: m/z = 489 [M^+]; Anal. Calcd. for $C_{17}H_{12}ON_2SCl_2I$: C, 41.64; H, 2.34; N, 5.75%. Found: C, 41.52; H, 2.58; N, 5.79%.

4e: Dark brown; IR (KBr): 3308 (−OH), 1618 (−C=N) cm^{-1}; ^1H NMR (DMSO-d_6): δ = 2.65 (s, 3H, CH_3), 7.18 (s, 1H, 5H of thiazole), 7.48–8.25 (m, 6H, Ar–H), 12.26 (s, 1H, OH, D_2O exchangeable), 10.60 (s, 1H, OH, D_2O exchangeable); EIMS: m/z = 379 [M^+]; Anal. Calcd. for $C_{17}H_{12}O_2N_2SCl_2$: C, 53.72; H, 3.15; N, 7.36%. Found: C, 53.38; H, 3.28; N, 7.19%.

4f: Pale brown; IR (KBr): 3234 (−OH), 1612 (−C=N) cm^{-1}; ^1H NMR (DMSO-d_6): δ = 1.95 (s, 3H, CH_3), 7.25 (s, 1H, 5H of thiazole), 7.48–8.10 (m, 6H, Ar–H), 12.26 (s, 1H, OH, D_2O exchangeable), 10.30 (s, 1H, OH, D_2O exchangeable); EIMS: m/z = 344 [M^+]; Anal. Calcd. for $C_{17}H_{13}O_2N_2SCl$: C, 58.30; H, 3.66; N, 8.10%. Found: C, 57.58; H, 3.28; N, 7.94%.

4g: Light pale brown; IR (KBr): 3232 (−OH), 1599 (−C=N) cm^{-1}; ^1H NMR (DMSO-d_6): δ = 2.20 (s, 3H, CH_3), 7.05 (s, 1H, 5H of thiazole), 7.58–8.12 (m, 6H, Ar–H), 12.18 (s, 1H, OH, D_2O exchangeable), 10.45 (s, 1H, OH, D_2O exchangeable); ^{13}C NMR: δ = 18, 115, 116, 118, 122, 119.3, 124, 129, 143, 152, 161, 163, 173; EIMS: m/z = 413 [M^+]; Anal. Calcd. for $C_{17}H_{11}O_2N_2SCl_3$: C, 49.72; H, 2.25; N, 5.36%. Found: C, 50.58; H, 3.01; N, 5.94%.

4h: Light pale brown; IR (KBr): 3142 (−OH), 1612 (−C=N) cm^{-1}; ^1H NMR (DMSO-d_6): δ = 1.95 (s, 3H, CH_3), 7.25 (s, 1H, 5H of thiazole), 7.48–8.10 (m, 6H, Ar–H), 12.05 (s, 1H, OH, D_2O exchangeable), 10.34 (s, 1H, OH, D_2O exchangeable); EIMS: m/z = 505 [M^+]; Anal. Calcd. for $C_{17}H_{11}O_2N_2SCl_2I$: C, 40.72; H, 2.15; N, 5.36%. Found: C, 43.58; H, 3.28; N, 6.14%.

4i: Pale brown; IR (KBr): 3230 (−OH), 1666 (−C=N) cm^{-1}; ^1H NMR (DMSO-d_6): δ = 1.88 (s, 3H, CH_3), 6.99 (s, 1H, 5H of thiazole), 7.48–7.90 (m, 6H, Ar–H), 12.11 (s, 1H, OH, D_2O exchangeable), 10.25 (s, 1H, OH, D_2O exchangeable); ^{13}C NMR: δ = 18, 88, 116, 119, 125, 126 127, 127.3, 129, 130, 132, 133, 139, 142, 162, 165, 171; EIMS: m/z = 505 [M^+]; Anal. Calcd. for $C_{17}H_{11}O_2N_2SCl_2I$: C, 40.72; H, 2.15; N, 5.36%. Found: C, 53.58; H, 3.28; N, 7.14%.

4m: Light pale brown; IR (KBr): 3142 (−OH), 1612 (−C=N) cm^{-1}; ^1H NMR (DMSO-d_6): δ = 1.95 (s, 3H, CH_3), 7.25 (s, 1H, 5H of thiazole), 7.48–8.10 (m, 6H, Ar–H), 10.78 (s, 1H, OH, D_2O exchangeable); EIMS: m/z = 373 [M^+]; Anal. Calcd. for $C_{17}H_{12}O_3N_3SCl$: C, 54.72; H, 3.15; N, 11.36%. Found: C, 53.58; H, 3.28; N, 10.14%.

Conclusion

In summary, we have described a novel and efficient method for the synthesis of thiazole derivatives by one-pot condensation of α-haloketones, thiourea, and substituted acetophenones using PEG-400 as a green reaction medium. The present procedure has the advantage of reduced reaction times, mild reaction conditions, high yields, and greener aspects such as avoiding hazardous organic solvent, ease of recovery, and reuse of reaction medium, thus making it a worthwhile addition to the existing methods.

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