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ORIGINAL PAPER

Dual nature of polyethylene glycol under microwave irradiation for the clean synthesis of oximes

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Abstract Polyethylene glycol (PEG-400 and PEG-600) is an efficient, inexpensive, and recyclable homogeneous medium and catalyst (dual nature) for the clean synthesis of oximes (and aldoximes) under microwave irradiation in the absence of acid and base catalysts. Both aliphatic and aromatic aldehydes/ketones give satisfactory results under microwave irradiation within a short time.

Keywords Oximes · PEG · Microwave energy · Recyclable

Introduction

The development of protocols for synthetic organic transformations with alternative reaction media to volatile organic compounds (VOCs) remains an ever-challenging objective [1, 2]. The unique solvent properties, higher solubilizing power, and cation coordination ability of polyethylene glycol (PEG) solutions make them useful as green solvents and phase transfer catalysts in organic synthesis [3]. PEGs are inexpensive, non-ionic, thermally stable, non-toxic, and recoverable media by phase separation methods. Unlike VOCs, low molecular weight liquid PEGs are non-volatile, biodegradable, and have low flammability. PEG has been found to be stable to acid, base, and high temperature [4, 5]. Both liquid and solid PEGs are highly soluble in water. Lower PEGs can be used as solvents in their own right with or without addition of water. PEGs exhibit different solubility in organic solvents; this property can enable the precipitation of PEGs from reaction mixtures in organic solvents for purification. The combined use of microwaves (MW) with PEGs as reaction media can accelerate organic reactions by the selective absorption of microwave energy by polar molecules. The short reaction time and selective product formation offered by microwave-assisted synthesis are suited to meet the increased demands of environmentally benign protocols.

The synthesis of oximes from aldehydes and ketones is a valuable organic transformation. Oximation is an efficient method for the characterization and purification of carbonyl compounds [6]. Oximes are more thermally stable than the corresponding carbonyl compounds and may be used as protecting groups, selective α-activating groups, and intermediates for the preparation of amides [7], nitriles [8], nitro compounds [9], and amines [10]. Oxime functionality is also an important structural feature in several biologically active compounds such as perillartine which is about 2,000 times as sweet as sucrose [11]. A number of methods [12–16] have been reported for the preparation of oximes catalyzed by both acids and bases, such as formic acid, pyridine/chloroform, ethanol/pyridine, and sulfuric acids and sodium hydroxide with or without solvent. The hazardous nature of these reagents results in many limitations. Therefore, many new strategies have recently been developed using solid acid catalysts [17] such as basic alumina, silica gel, Amberlyst A-21 in ethanol, CaO, TiO_2/SO_4^{2-} without solvent, nanostructured pyrophosphate, and ionic liquids under ultrasound irradiation.

In continuation of previous work [18], herein, we report PEG-400 and PEG-600 as recyclable homogeneous reaction media and catalysts for the preparation of oximes from aldehydes and ketones with hydroxylamine hydrochloride under microwave irradiation and thermal treatment without use of acid and base catalysts (Scheme 1).

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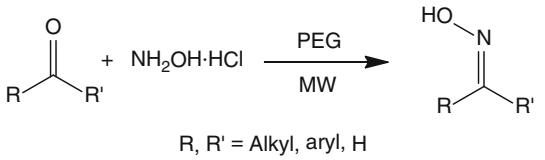
Scheme 1



Results and discussion

Our efforts began with the synthesis of benzophenone oxime from benzophenone (3 mmol) and hydroxylamine hydrochloride (3 mmol) in PEG-200, 400, and 600 as reaction media under microwave irradiation (Table 1). From these results, PEG-600 was found to be the best medium (Fig. 1) for the oxime synthesis.

The catalytic activity of polyethylene glycol for this reaction was again investigated using 0.5 and 1 cm^3 of PEGs at different power levels of microwave energy. The product yields increased with increasing microwave energies within the temperature range of 64–79 °C (Table 1); these yields were the same in both 0.5 and 1 cm^3 of PEG (Table 1, entries 1–5). Increasing microwave power causes more collisions between substrate molecules in the PEGs via a dipolar ionization mechanism resulting in increasing reaction temperature. Without PEG, no product formation was observed even at higher power level (Table 1, entry 6). All these observations indicate that the hydrophilic nature of PEGs is the driving force for this reaction under microwave irradiation wherein PEGs behave as both the medium and catalyst.

After optimization of the reaction conditions with 3 mmol of ketone, 3 mmol of hydroxylamine hydrochloride, and 0.5 cm^3 of PEG-600, we extended the above synthesis to different aliphatic and aromatic keto compounds using both thermal and microwave energies (Table 2) for comparative studies. However no product was obtained if the reaction was carried out by stirring at room temperature (Table 2, entry 7). The reaction of acetophenone did not give any product in the absence of 0.5 cm^3 of PEG under microwave irradiation (280 W) for 5 min. The turnover frequencies (TOF) were determined from GC analysis at the starting time for all reactions. The thermal conditions gave lower TOF and less yields of product at the same temperature than with microwave irradiation (Table 2). We observed higher TOF for all aliphatic keto compounds (Table 2, entries 1, 3, 5, 6) as compared to aromatic keto compounds (Table 2, entries 2, 4) under microwave irradiation. All keto compounds yielded excellent results within 2–5 min reaction time (Table 2). The results for the synthesis of aldoximes from aliphatic and aromatic aldehydes using standard conditions

Table 1 Optimization of the reaction with PEGs for the synthesis of benzophenone oxime under microwave irradiation within 5 min at different temperatures

Entry	MW power/W	Amount of PEG/cm^3	Temp./°C	Product yield/%[a,b]		
				PEG-200	PEG-400	PEG-600
1	280	1	64	25	30	65
		0.5			29	65
2	350	1	67	30	40	94
		0.5			40	94
3	420	1	70	40	55	95
		0.5			54	94
4	490	1	75	45	75	95
		0.5			74	95
5	560	1	79	50	85	95
		0.5			84	94
6	560	0	66	–	–	–

[a] Isolated yield

[b] Using 3 mmol of benzophenone and 3 mmol of hydroxylamine hydrochloride in PEGs

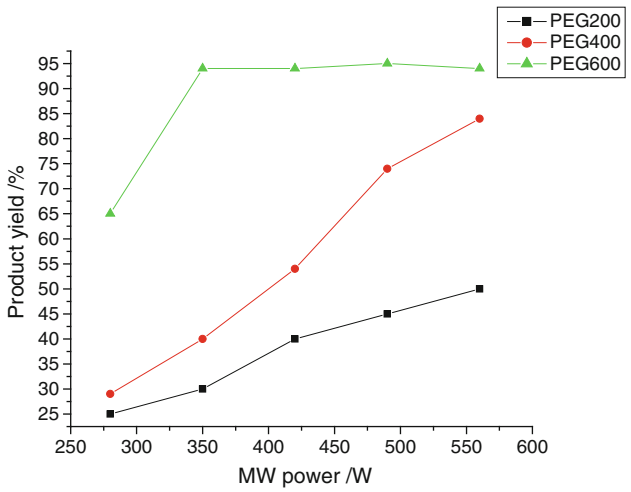


Fig. 1 Comparison of the yields of benzophenone oxime against microwave power in 0.5 cm^3 PEG

are included in Table 3. In the presence of strong electron-donating groups, the aldehyde molecules were found to be inactive (Table 3, entries 8, 9) at higher microwave energies. All other aldehyde molecules yielded good to excellent results within 2–6 min at different microwave energies (Table 3). The TOF also increased in the case of 4-nitrobenzaldehyde and 4-chlorobenzaldehyde with an increase of the microwave power from 280 W to 350 W (Table 3, entries 4, 7). The used PEG is recovered from the aqueous solution by evaporation of water under reduced pressure and used again for the next reaction cycle without

Table 2 Synthesis of oximes in PEG-600 under microwave and thermal conditions

Entry	Ketone	MW/W	Temp./°C	Product m.p./°C (lit)[a]	Time/min		Product yield/%[b,c,d]			
					MW	Thermal	MW	MW TOF (% conversion)	Thermal	Thermal TOF (% conversion)
1	Cyclohexanone	280	60	87 (91)	2	30	90	165.2 (45.9)	65	6.5 (1.8)
2	Acetophenone	280	60	58 (59)	5	50	91	42.1 (11.7)	50	0
3	Acetone	280	42	59 (60)	2	20	88	159.4 (44.3)	65	9.7 (2.7)
4	Benzophenone	350	67	143 (144)	5	2 h	94	54 (15)	70	0
5	Cyclopentanone	280	70	54 (55)	3	50	95	106.5 (29.6)	60	3.96 (1.1)
6	Ethyl methyl ketone	280	44	Liq. (−30)	3	30	85	102.6 (28.5)	50	5.4 (1.5)
7	Benzophenone	–	25		–	24 h	–	–	NR	–

[a] Literature data [19–22]

[b] Isolated yield

[c] Turnover frequency = (mmol of product/amount of PEG in cm^3) h^{-1}

[d] Conversion calculated with GC analysis during the first minute

Table 3 Synthesis of aldoximes in PEG-600 under microwave irradiation

Entry	Aldehydes	MW/W	Temp./°C	Time/min	Product m.p./°C (lit)[a]	Product yield[b]/%	TOF[c] (% conversion)[d]
1	Benzaldehyde	280	60	2	Liq. (−35)	90	158.7 (44.1)
2	2-Nitrobenzaldehyde	350	70	3	97 (98)	98	123.2 (34.2)
3	4-Nitrobenzaldehyde	280	70	5	132 (133)	98	70.2 (19.5)
4	4-Nitrobenzaldehyde	350	75	2	132 (133)	97	177.1 (49.2)
5	3-Nitrobenzaldehyde	560	65	5	121 (122)	70	268 (74.5)
6	4-Chlorobenzaldehyde	280	62	6	105 (107)	80	48.6 (13.5)
7	4-Chlorobenzaldehyde	350	66	2	105 (107)	96	332.2 (92.3)
8	4-Hydroxybenzaldehyde	560	60	5	–	NR	0
9	4-Methoxybenzaldehyde	560	56	5	–	NR	0
10	4-Methylbenzaldehyde	490	65	5	78 (80)	75	77.4 (21.5)
11	Furaldehyde	490	75	2	71 (72)	97	243.3 (67.6)
12	Cinnamaldehyde	490	76	2	137 (139)	85	153 (42.5)
13	Butanal	350	78	2	− (29)	94	169.2 (47)
14	Pentanal	350	80	2	− (52)	96	173.5 (48.2)
15	D-Glucose	280	65	2	–	Decomposed	–
16	Acrolein	280	50	2	–	Polymeric	–
17	2,2-Dimethyl-1,3-dioxolane-4-carbaldehyde	350	70	3	–	Trace	–

[a] Literature data [19–22]

[b] Isolated yield

[c] Turnover frequency = (mmol of product/amount of PEG in cm^3) h^{-1}

[d] Conversion calculated with GC analysis during the first minute

loss of activity. The same recovered PEG is utilized for five cycles of reactions for the preparation of benzophenone oxime.

Conclusion

This work focuses on the dual nature of PEGs as an efficient, inexpensive, and recyclable homogeneous medium and catalyst under microwave irradiation for the synthesis of oximes from carbonyl compounds and hydroxylamine hydrochloride. This method offers a rapid and clean alternative and reduces reaction times, thus fulfilling several requirements of green chemistry.

Experimental

^1H and ^{13}C NMR spectra were recorded on a JEOL JNM ECS-400 MHz FT-NMR spectrometer from solution in

$CDCl_3$ with TMS as the internal standard. IR spectra were recorded on a Nicolet Impact-410 spectrophotometer. The GC–MS spectra and percentage conversion for TOF at the starting time were recorded by an Perkin Elmer Clarus 600 apparatus. Microwave-assisted reactions were carried out in open glass tubes using a mono mode microwave reactor (catalyst system). All chemicals are commercially available and were used without further purification.

General procedure for the synthesis of oximes under microwave irradiation

Typical reactions were carried out as follows under microwave/thermal conditions: A finely powdered mixture of 3 mmol of aldehyde or ketone and 3 mmol of hydroxylamine hydrochloride in 0.5 cm^3 of PEG-600 was placed in an open glass tube (or heated classically in an oil bath) in a mono mode microwave reactor and irradiated at various power levels with the monitoring of the specified temperature. The progress of the reaction was monitored using thin-layer chromatography (TLC). After completion, the reaction mixture was diluted with 5 cm^3 of distilled water and the product was extracted from the aqueous solution with diethyl ether (3×4 cm^3) or any other organic solvent (whichever is applicable). The ether extract was dried over anhydrous Na_2SO_4 and evaporated under reduced pressure. For spectroscopic analysis, the product is further purified by TLC techniques using hexane and ethyl acetate as the mobile phases. The recovered PEG retained its activity for several cycles. All synthesized products are reported in the literature [19–22] and were fully characterized by spectral analysis.

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