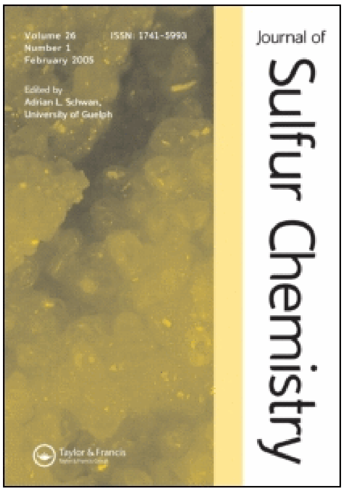

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An environmental-benign approach for the synthesis of alkylthiocyanates

Suman Awasthi[a]; Ambati Narasimha Rao[a]; Kumaran Ganesan[a]
[a] Synthetic Chemistry Division, Defence Research and Development Establishment, Gwalior, India

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An environmental-benign approach for the synthesis of alkylthiocyanates

Suman Awasthi, Ambati Narasimha Rao and Kumaran Ganesan*

Synthetic Chemistry Division, Defence Research and Development Establishment, Jhansi Road, Gwalior 474002, India

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Owing to the present environmental awareness, attempts are being made toward the evolution of environmentally benign processes using aqueous media and microwave-assisted reactions. A new paradigm for the synthesis of alkyl thiocyanates using polyethylene glycol (PEG)-water as benign reaction medium is described, with the compounds readily accessible in high purity within 2–3 h by conventional heating procedure. Alternatively, a further simple, time-saving microwave irradiation method is also described using PEG as phase transfer catalyst.

Keywords: microwaves; solvent free; polyethylene glycol; phase transfer catalyst; alkyl thiocyanate

Alkyl thiocyanates are one of the most important synthetic intermediates for the preparation of sulfur-containing organic compounds (*1*). Not only natural products containing the thiocynate group have attracted attention (*2, 3*), but this functional group can also be used as a masked mercapto group or a precursor for sulfur-containing heterocycles (*4*), and thiocyanates have traditionally been used as pesticides (*5, 6*). Yet the low nucleophilicity of the –SCN ion requires relatively harsh reaction conditions. Moreover, the thiocyanate group is poorly stable when heated or submitted to acidic conditions. Ammonium thiocyanate was used successfully in nucleophilic substitution reaction; but this reagent is sensitive and explosion hazards have been reported (*7, 8*). Thiocyanates can be obtained from alcohols (*9, 10*), silylethers (*11*) using *in situ* formed electrophilic phosphorane $Ph_3P(SCN)_2$ or amines (*12*). However, the results are unreliable and not reproducible because of the low thermal stability of the required intermediate $(SCN)_2$, and also various amounts of rearranged isothiocyanate by-product are formed. The toxicity of the starting material, $Ph_3P(SCN)_2$ is also a major drawback in this thiocyanation method (*13*).

In recent years, environmentally friendly synthetic methods have received considerable attention. Regulatory pressure is increasingly focusing on the use, manufacture and disposal of organic solvents, and thus the development of nonhazardous alternatives is vitally important for the continued and sustainable development of the chemical enterprise (*14, 15*). There are many advantages in replacing volatile organic solvents with water or various types of aqueous solutions. The most

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*Corresponding author. Email: ganesan_kumaran@hotmail.com

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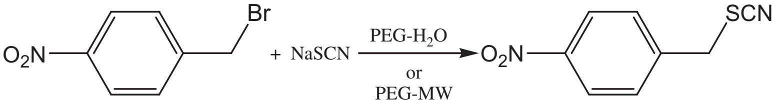
obvious are low cost, reduced fire hazard, low toxicity and fewer environmental risks as a result of discharge of supporting phase. Water and aqueous-based solvent systems may represent an increasingly significant choice for the replacement of traditional solvents in synthetic organic chemistry (*16, 17*). Thus the use of aqueous polyethylene glycol (PEG) solutions and related materials in chemical reactions has attracted much attention of chemists who are forced to change old themes with new twists to develop environmentally friendly processes.

This is despite the fact that unlike several of the "neoteric solvents" such as ionic liquids where toxicity-environmental burden data are unknown, complete toxicity profiles are available for a range of PEG molecular weights, and many are already approved for internal consumption (*18–20*). In this context, PEG has been used as a recyclable reaction medium (*21*) and phase-transfer catalyst (PTC) in much organic synthesis. A number of recent reviews have also covered PEG chemistry and its applications in biotechnology and medicine (*22, 23*), PEG and PEG-supported catalysis (*24*), and PEG and its derivatives as solvent and PTC in organic synthesis (*25, 26*). PEG also has low flammability, and is biodegradable. PEG may be recovered from aqueous solution by extraction with a suitable solvent or by direct distillation of water or solvent (*27*). With the increase in the global population, obviously, demands have increased to meet requirements. Industries are producing in bulk at the cost of huge waste, which makes the environment polluted. This led us to develop a new simple greener method for the synthesis of alkyl thiocyanates.

In view of the emerging importance of green solvent in organic synthesis, we report herein PEG-water as a recyclable reaction medium for the synthesis of alkyl thiocyanates, which is designed to circumvent additional purification steps, and also describe the use of solventless conditions. The high yields and overall low-waste generation of these approaches give them attractive green chemistry metrics, along with remarkable versatility. Typically, alkyl bromide and 1.5 molar equivalents of the sodium thiocyanate were heated in the minimal volume of water containing catalytic amount of PEG-400, and stirred until the reaction was completed as determined by gas chromatography (GC) or thin layer chromatography (TLC) monitoring. The pure product precipitates/separates out of the reaction medium on cooling, and was easily be collected by vacuum filtration. Synthesis of 4-nitrobenzyl thiocyanate is shown in Scheme 1 as a representative example.

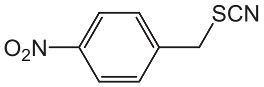
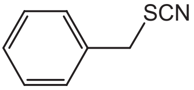
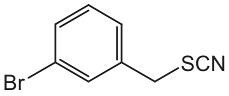
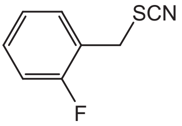
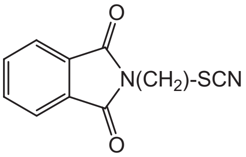
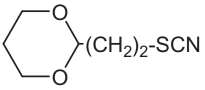
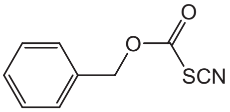
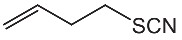
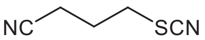
The water is then removed from the PEG by vacuum and on cooling the remaining PEG, whereby sodium bromide separates out. The PEG and water were reused continuously in the repeated runs by the same procedure for the preparation of representative alkyl thiocyanate. Thus, various alkyl thiocyanates (Table 1, Entry 1–9) were prepared by this environmental and eco-friendly procedure. Interestingly, other functional groups such as cyanide, double bond, phenyl halide, aromatic nitrite, ester, dioxolane and amide were not affected in these nucleophilic substitution reactions.

The application of microwave irradiation as a nonconventional energy source for activation of reaction has now become a very popular and useful technology in organic chemistry (*28–36*). The combination of microwave irradiation and water-free reaction conditions leads to enhanced reaction rates and higher yields of pure products. In the solvent free preparation of **1**–**9**, the alkyl thiocyanates were obtained in almost quantitative yield by low-intensity grinding of the alkyl bromide with 1.5 molar equivalents of sodium thiocyanate using pestle and mortar over a period of 5 min, then PEG-400 was added in a catalytic amount and again the mixture was agitated for a



Scheme 1. Synthesis of 4-nitrobenzyl thiocyanate.

Table 1. Synthesis of alkyl thiocyanates.

		Reaction time		Yield (%)[b]	
Entry	Product[a]	Conventional (hrs)	MW (min)	Conventional	MW[c]
1.		2	4	70	98
2.		2	5	65	95
3.		3	8	65	88
4.		3	8	65	95
5.		2	5	70	90
6.		3	8	70	90
7.		2	4	70	95
8.		3	10	55	75
9.		2	5	70	95

Notes: [a]All the products were characterized by ^{1}H NMR, IR, MS. [b]Isolated yields. [c]MW, microwave.

while and placed inside the microwave oven and irradiated at 180 W for specified time (Table 1). After completion of the reaction, the product was precipitated out by addition of water and was separated easily. Again the water was removed from the PEG under vacuum.

In summary, we have demonstrated the use of PEG as PTC in microwave-assisted synthesis as well as the use of PEG-aqueous medium for conventional method of synthesis of various kinds of alkyl thiocyanates. We have developed a simple, efficient, economical and ecofriendly process for the synthesis that does not require any organic solvent, and water used in reaction media can also be recycled, which enhances the green perspective. This method can be easily upscaled to bulk production of alkyl thiocyanates for industrial applications.

Experimental

General procedure

Conventional method

Synthesis of 4-nitrobenzyl thiocyanate is given as a representative example. A mixture of 4-nitrobenzyl bromide (0.216 g, 1 mmol) and sodium thiocyanate (0.122 g, 1.5 mmol) was stirred in a small amount of water (1 ml) in the presence of PEG 400 (0.02 g, 0.05 mmol) as PTC at 60–70°C for 2 h. The crystalline powder was collected by vacuum filtration, washed with water and dried in a desiccator to give 4-nitrobenzyl thiocyanate (yield 90%).

Microwave-assisted synthesis of alkyl thiocyanates: 4-nitrobenzyl bromide (0.216 g, 1 mmol), sodium thiocyanate (0.122 g, 1.5 mmol) and PEG 400 (0.02 g, 0.05 mmol) were taken in a conical flask, mixed thoroughly and subjected to microwave irradiation at 180 W for 1 min. The reaction was monitored by GC, then thoroughly mixed outside the MW and again irradiated for another 1 min. This was repeated for the total radiation time (Table 1). After completion of the reaction, water (1 ml) was added to the reaction mixture and stirred well. The precipitate thus obtained was washed with water to give solid product. Further pure product was obtained by recrystallization from ethanol. The products thus obtained were characterized by comparison of their ^{1}H NMR, IR and MS, the spectral data of all the products were identical with those of authentic samples.

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