Revisiting Nucleophilic Substitution Reactions: Microwave-Assisted Synthesis of Azides, Thiocyanates, and Sulfones in an Aqueous Medium

Yuhong Ju,[†] Dalip Kumar,[‡] and Rajender S. Varma*[,†]

Clean Processes Branch, Sustainable Technology Division,
National Risk Management Research Laboratory,
U.S. Environmental Protection Agency, 26 West Martin Luther
King Drive, MS 443, Cincinnati, Ohio 45268, and
Chemistry Group, Birla Institute of Technology and Science,
Pilani 333031, Rajasthan, India

ju.yuhong@epa.gov; dalipk@bits-pilani.ac.in;
varma.rajender@epa.gov

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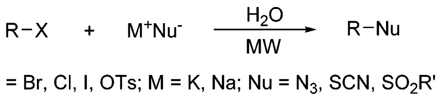


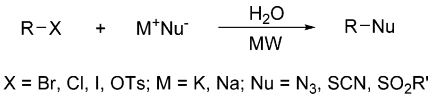
$$R{-}X \quad + \quad M^{+}Nu^{-} \xrightarrow[MW]{H_2O} R{-}Nu$$

X = Br, Cl, I, OTs; M = K, Na; Nu = N_3, SCN, SO_2R'

A practical, rapid, and efficient microwave (MW) promoted synthesis of various azides, thiocyanates, and sulfones is described in an aqueous medium. This general and expeditious MW-enhanced nucleophilic substitution approach uses easily accessible starting materials such as halides or tosylates in reaction with alkali azides, thiocyanates, or sulfinates in the absence of any phase-transfer catalyst, and a variety of reactive functional groups are tolerated.

Reactions in aqueous media are of paramount importance in organic syntheses.[1] The use of many toxic and volatile organic solvents, particularly chlorinated hydrocarbons, as reaction media contributes pollution to the environment, and it is highly desirable to develop environmentally benign processes that can be conducted in aqueous media. Furthermore, using water as a solvent offers many advantages such as simple operation and high efficiency in many organic reactions that involve water-soluble substrates and reagents. Organic reactions assisted by microwave (MW) irradiation have attracted considerable attention in the past two decades for the efficient and relatively friendlier synthesis of a variety of organic compounds.[2] Developing efficient, selective, and eco-friendly synthetic methods for applications in organic synthesis is an ongoing program in our research group.[1c,e,2a,d] Utilization of water as reaction media[3] in conjunction with microwave irradiation[4] is one of the emerging nonconventional methods being recognized as viable environmentally benign alternatives.[5]

SCHEME 1. Microwave-Enhanced Nucleophilic Substitution Reactions



$$R{-}X \quad + \quad M^{+}Nu^{-} \xrightarrow[MW]{H_2O} R{-}Nu$$

X = Br, Cl, I, OTs; M = K, Na; Nu = N_3, SCN, SO_2R'

In the continuation of our studies on microwave-assisted organic synthesis in an aqueous medium,[4] we have broadened our interest to nucleophilic substitution reactions which could possibly be accelerated under this alternative mode of activation. Herein, we wish to report the nucleophilic substitution reaction of alkyl halides or tosylates using readily available alkali azides, thiocyanates, and sulfinates under microwave irradiation that proceed safely and efficiently in aqueous media for the preparation of various azides, thiocyanates, and sulfones (Scheme 1).

Organic azides, an important class of energy-rich and flexible intermediate compounds,[6] have drawn considerable interest since the late 19th century.[7] Industrial interest in organic azides began with the use of azides as a precursor for the synthesis of amines[8] and heterocycles such as triazoles and tetrazoles[9] as well as their application as blowing agents and functional groups in pharmaceuticals as exemplified by azidonucleosides in the treatment of AIDS[10] and their bioconjugation via Staudinger ligation.[11] The most common route to alkyl azides involves the classic nucleophilic substitution reaction of alkyl halides with inorganic azides[6c] but suffers from complex procedures,[12] long reaction

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[*] To whom correspondence should be addressed. Tel: (+1-513) 487-2701. Fax: (+1-513) 569-7677.

[†] U.S. Environmental Protection Agency.

[‡] Birla Institute of Technology and Science.

(1) (a) Li, C. J. *Chem. Rev.* **2005**, *105*, 3095. (b) *Organic Synthesis in water*; Grieco, P. A., Ed.; Blackie: London, 1998. (c) Wei, W.; Keh, C. C. K.; Li, C. J.; Varma, R. S. *Clean Technol. Environ. Policy* **2005**, *7*, 62. (d) Narayan, S.; Muldoon, J.; Finn, M. G.; Fokin, V. V.; Kolb, H. C.; Sharpless, K. B. *Angew. Chem., Int. Ed.* **2005**, *44*, 3275. (e) Skouta, R.; Varma, R. S.; Li, C. J. *Green Chem.* **2005**, *7*, 571.

(2) (a) Varma, R. S. *Advances in Green Chemistry: Chemical Syntheses Using Microwave Irradiation*; AstraZeneca Research Foundation India: Bangalore, India, 2002. (b) Gabriel, S. C.; Gabriel, S.; Grant, E. H.; Halstead, B. S. J.; Mingos, D. M. P. *Chem. Soc. Rev.* **1998**, *27*, 213. (c) Loupy, A., Ed. *Microwaves in Organic Synthesis;* Wiley-VCH: Weinheim, 2002. (d) Varma, R. S. *Green Chem.* **1999**, *1*, 43. (e) de la Hoz, A.; Díaz-Ortiz, A’.; Moreno, A. *Chem. Soc. Rev.* **2005**, *34*, 164. (f) Varma, R. S. *Microwave Technology − Chemical Applications: Kirk-Othmer Encyclopedia of Chemical Technology*, 5th ed.; John Wiley & Sons: New York, 2004.

(3) (a) Kappe, C. O. *Angew. Chem., Int. Ed.* **2004**, *43*, 6250. (b) Jachuck, R. J. J.; Selvaraj, D. K.; Varma, R. S. *Green Chem.* **2006**, *8*, 29. (c) Bose, A. K.; Manhas, M. S.; Ganguly, S. N.; Sharma, A. H.; Banik, B. K. *Synthesis* **2002**, 1578. (d) Baghurst, D. R.; Mingos, D. M. P. *Chem. Soc. Rev.* **1991**, *20*, 1. (e) Leadbeater, N. E. *Chem. Commun.* **2005**, 2881. (f) An, J.; Bagnell, L.; Cablewski, T.; Strauss, C. R.; Trainor, R. W. *J. Org. Chem.* **1997**, 62, 2505.

(4) (a) Ju, Y.; Varma, R. S. *Org. Lett.* **2005**, *7*, 2409. (b) Ju, Y.; Varma, R. S. *J. Org. Chem.* **2006**, *71*, 135. (c) Ju, Y.; Varma, R. S. *Green Chem.* **2004**, *6*, 219.

(5) (a) Varma, R. S.; Naicker, K. P. *Tetrahedron Lett.* **1998**, *39*, 2915. (b) Varma, R. S.; Naicker, K. P.; Kannan, P.; Aschberger, J. *Synth. Commun.* **1999**, *29*, 2823. (c) Varma, R. S.; Naicker, K. P.; Kumar, D. *J. Mol. Catal. A: Chem.* **1999**, *149*, 153.

(6) (a) Smith, P. A. S. *Org. React.* **1946**, *3*, 337. (b) Boyer, J. H.; Canter, F. C. *Chem. Rev.* **1954**, *54*, 1. (c) Scriven, E. F. V.; Tumbull, K. *Chem. Rev.* **1988**, *88*, 297.

(7) (a) Grie*β*, P. *Philos. Trans. R. Soc. London* **1864**, *13*, 377. (b) Curtius, T. *Ber. Dtsch. Chem. Ges.* **1890**, *23*, 3023.

(8) Rao, H. S. P.; Siva, P. *Synth. Commun.* **1994**, *24*, 549.

(9) (a) Bräse, S.; Gil, C.; Knepper, K.; Zimmermann, V. *Angew. Chem., Int. Ed.* **2005**, *44*, 5188. (b) Kolb, H. C.; Sharpless, K. B. *Drug Discovery Today* **2003**, *8*, 1128.

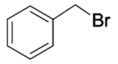
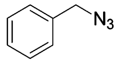
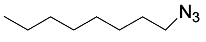
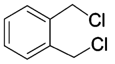
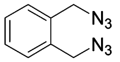
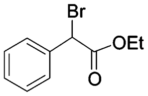
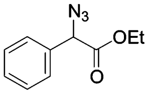
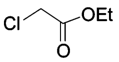
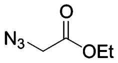
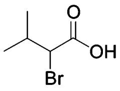
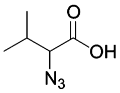
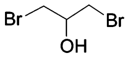
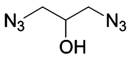
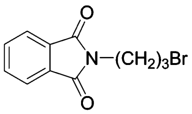
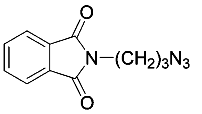
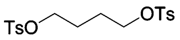
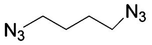
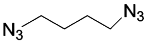
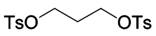
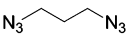
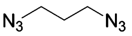
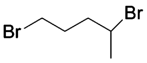
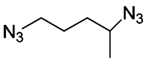
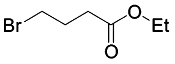
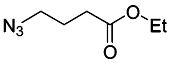
(10) Lin, T. S.; Prusoff, W. H. *J. Med. Chem.* **1978**, *21*, 109.

(11) Kohn, M.; Breinbauer, R. *Angew. Chem., Int. Ed.* **2004**, *43*, 3106.

(12) (a) Lieber, E.; Chao, T. S.; Rao, C. N. R. *J. Org. Chem.* **1957**, *22*, 238. (b) Ito, M.; Koyakumaru, K.; Ohta, T.; Takaya, H. *Synthesis* **1995**, 376.

10.1021/jo061114h CCC: $33.50

TABLE 1. Microwave-Accelerated Rapid Synthesis of Azides[a]

Entry	*Halides/Tosylates*	*Products*[b]	*IR (cm^{-1})*	*Yields (%)*[c]
1		 **(1a)**	2099	95
2	$C_8H_{17}Br$	 **(1b)**	2157	87[d]
3		 **(1c)**	2099	95
4		 **(1d)**	2106	81
5		 **(1e)**	2106	53
6		 **(1f)**	2108	47
7		 **(1g)**	2102	99
8		 **(1h)**	2096	88
9		 **(1i)**	2060	77
10	$Br(CH_2)_4Br$	 **(1i)**	2060	89
11		 **(1j)**	2098	60
12	$Br(CH_2)_3Br$	 **(1j)**	2098	78
13		 **(1k)**	2097	82
14		 **(1l)**	2096	87

[a] All reactions were carried out using 1 mmol of halides/1.3 mmol of sodium azide, MW power 70−100 W, at 120 °C for 30 min. [b] The NMR spectra of all synthesized alkyl azides are in accord with the literature. [c] Isolated yields are based on starting halides/tosylates. [d] GC/MS yield based on starting halides.

times,[13] low yields,[12] and most importantly the danger of explosion at elevated temperature and in halogenated solvents.[14]

The MW-assisted reaction of different halides/tosylates with sodium azide was examined in an aqueous medium without using the phase-transfer catalyst.[5] It was found that the reaction of halides/tosylates with sodium azide is fairly general (Table 1) and tolerates a variety of functional groups such as ester, carboxylic acid, hydroxyl, and imide (entries 4−8). Though tosylate is believed to be a better leaving group than bromide, the liquid/liquid biphasic reaction is more favored than the solid/liquid/liquid triphasic reaction as in the trend shown between ditosylate (solid) and dihalide (liquid) (entries 9−12). The selection of water as the reaction medium also offered a safer experimental procedure to prevent the potential explosion danger of azidation in a halogenated solvent.[14,15]

After the successful synthesis of various azides and to generalize the protocols for the nucleophilic substitution reactions in an aqueous medium, the synthesis of thiocyanates was undertaken. Thiocyanates are well-known in the area of organosulfur chemistry and widely used as key intermediates in various organic transformations[16] and as biocides.[17] Thiocyanates are also considered to be an important class of compounds found in some anticancer natural products formed by deglycosylation of glucosinolates derived from cruciferous vegetables. Further, α-thiocyanato carbonyl compounds are the preferred substrates for the synthesis of thiazoles of various herbicidal and related biological activities. The MW-assisted nucleophilic substitution of sodium/potassium thiocyanate with different halides/tosylates

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(13) Heathcock, C. H. *Angew. Chem., Int. Ed. Engl.* **1969**, *8*, 134.

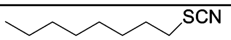
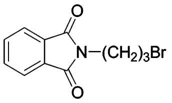
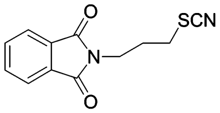
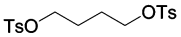
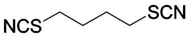
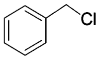
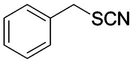
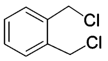
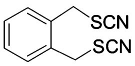
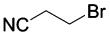
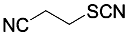
(14) (a) Peat, N. P.; Weintraub, P. M. *Chem. Eng. News* **1993**, April 19, 4. (b) Hruby, V. J.; Biteju, L.; Li, G. *Chem. Eng. News* **1993**, Oct. 11, 2.

(15) Guy, R. G. Syntheses and Preparative Applications of Thiocyanates. In *The Chemistry of Cyanates and their Derivatives*; Patai, S., Ed.; Wiley: Chichester, 1977; p 1003.

(16) Magnus, P. D. *Tetrahedron* **1977**, *33*, 2019.

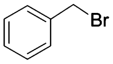
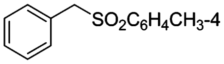
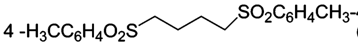
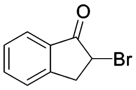
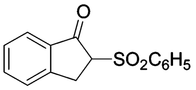
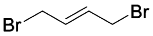
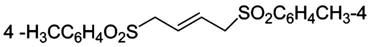
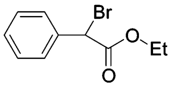
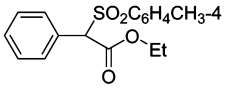
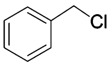
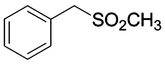
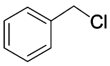
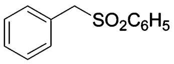
(17) Ogura, K. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon Press: Oxford, 1991; Vol. 1, p 505.

TABLE 2. Microwave-Accelerated Rapid Synthesis of Thiocyanates[a]

Entry	*Halides/Tosylates*	*Products*[b]	*Yields (%)*[c]
1	$C_8H_{17}Br$	 **(2a)**	86
2		 **(2b)**	90
3		 **(2c)**	78
4		 **(2d)**	95
5		 **(2e)**	91
6		 **(2f)**	85

[a] All reactions were carried out using 1 mmol of halides/1.3 mmol of potassium thiocyanate, MW power 70−100 W, at 110 °C for 20 min. [b] The NMR spectra of all synthesized alkylthiocyanates are in accord with the literature. [c] Isolated yields are based on starting halides/tosylates.

TABLE 3. Microwave-Accelerated Rapid Synthesis of Sulfones[a]

Entry	*Halides*	*Sodium sulfinate*	*Products*[b]	*Yields (%)*[c]
1	$C_8H_{17}Br$	$4\text{-}CH_3C_6H_4SO_2Na$	$4\text{-}CH_3C_6H_4SO_2C_8H_{17}$ **(3a)**	81
2		$4\text{-}CH_3C_6H_4SO_2Na$	 **(3b)**	88
3	$Br(CH_2)_4Br$	$4\text{-}CH_3C_6H_4SO_2Na$	 **(3c)**	70
4		$C_6H_5SO_2Na$	 **(3d)**	91
5		$4\text{-}CH_3C_6H_4SO_2Na$	 **(3e)**	85
6		$4\text{-}CH_3C_6H_4SO_2Na$	 **(3f)**	85
7		CH_3SO_2Na	 **(3g)**	82
8		$C_6H_5SO_2Na$	 **(3h)**	85

[a] All reactions were carried out using 1 mmol of halides/1.3 mmol of alkylsulfinic acid, sodium salt, MW power 70−100 W, at 120 °C for 30 min. [b] The NMR spectra of all synthesized alkyl sulfones are in accord with the literature. [c] Isolated yields are based on starting halides.

in water was also investigated, and the reactions proved very successful with the formation of alkylthiocyanate in good to excellent yields (Table 2); no significant rearrangement to isothiocyanate was observed.

Finally, we extended this environmentally benign protocol to the synthesis of sulfones which can be transformed to many other groups.[18] Some leading examples include the importance of sulfonyl carbanions and their intriguing stereochemical characteristics:[19] the addition of heteroatom nucleophiles, nonstabilized organometallics, and enolate-stabilized carbon nucleophiles to α,β-unsaturated sulfones.[20] The application of sulfones in organic synthesis has especially proven valuable in many of the most demanding and sophisticated total syntheses conducted.[21] The competition of sulfur alkylation to afford sulfone, or of oxygen alkylation to generate sulfinate ester, is another reason to search for alternative milder reaction conditions that can deliver higher yields of sulfones.[22] The aqueous

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(18) De Lucchi, O.; Pasquato, L. *Tetrahedron* **1988**, *44*, 6755.

(19) Dharanipragada, R.; VanHulle, K.; Bannister, A.; Bear, S.; Kennedy, L.; Hruby, V. J. *Tetrahedron* **1992**, *48*, 4733.

(20) Edwards, J. O.; Pearson, R. G. *J. Am. Chem. Soc.* **1962**, *84*, 16.

(21) Simpkins, N. S. *Sulfones in Organic Synthesis*, *Tetrahedron organic chemistry series*; Pergamon Press: New York, 1993, Vol. 10.

MW-assisted preparation of alkyl sulfones demonstrated herein is very simple and efficient and affords good to excellent product yields in less than 30 min (Table 3).

In conclusion, this microwave-assisted synthesis of azides, thiocyanates, and sulfones has been developed and proved to be a useful alternative which avoids the use of environmentally detrimental volatile chlorinated hydrocarbons. All the reactions with readily available halides or tosylates have shown a significant increase in reactivity thus reducing the reaction times with substantial improvement in the yields. Various functional groups such as ester, carboxylic acid, carbonyl, and hydroxyl were unaffected under the mild reaction conditions employed. This method involves simple experimental procedures and product isolation which avoids the use of phase-transfer catalysts and is expected to contribute to the development of a greener strategy for the preparation of various azides, thiocyanates, sulfones, and other useful compounds.

Experimental Section

The representative experimental procedure is as follows: 1,4-dibromobutane (1 mmol, 0.215 g) and sodium azide (2.5 mmol, 0.163 g) in water (2 mL) were placed in a 10 mL crimp-sealed thick-walled glass tube equipped with a pressure sensor and a magnetic stirrer. The reaction tube was placed inside the cavity of a CEM Discover focused microwave synthesis system, operated at 120 ± 5 °C (temperature monitored by a built-in infrared sensor), power of 70−100 W, and a pressure of 60−100 psi for 30 min. After completion of the reaction, diethyl ether was added to extract the alkyl azide. GC/MS analysis indicated the disappearance of alkyl halides. The FT-IR spectrum of the crude product was obtained using a FT-IR spectrometer, and the formation of alkyl azide was confirmed by the characteristic IR adsorption around 2100 cm^{-1}. Removal of the solvent under reduced pressure (rotary evaporator) afforded the product, 1,4-diazido-butane (0.125 g) in 89% yield. ^{1}H and ^{13}C NMR were recorded in chloroform-*d* ($CDCl_3$) with TMS as an internal reference using a 300 MHz NMR spectrometer and were consistent with the literature.

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Supporting Information Available: Experimental procedures, NMR spectrum, and melting points for synthesized compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

JO061114H

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(22) (a) Field, L.; Clark, R. D. *Org. Synth., Coll. Vol. IV* **1963**, 674. (b) Sukata, K. *Bull. Chem. Soc. Jpn*. **1984**, *57*, 613.