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Microwave Assisted Sulfopropylation of *N*-Heterocycles Using 1,3-Propane Sultone

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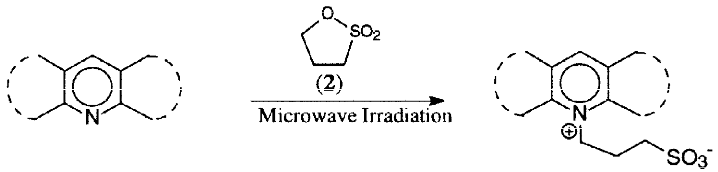
Abstract: *Dramatic rate acceleration was observed for N-sulfopropylation of heterocyclic compounds (* ***1a-h****) using 1,3-propane sultone(2) under microwave irradiation affording the N-sulfopropylated compounds (* ***3a-h****) in 68-95% yield.* © 1998 Elsevier Science Ltd. All rights reserved.

Water solubility of organic molecules is frequently required for their biological evaluation, and various commercial applications. Sulfopropyl group has been employed extensively to improve hydrophilicity and thereby aqueous solubility of a variety of compounds such as dyes,[1a,b] nucleosides,[2] proteins,[3a,b] and polymers.[3c,d] Sulfopropylated derivatives of fatty acids have been shown to have antistatic properties[4] and, *N*-sulfopropylated acridines have been recently introduced as chemiluminescent probes in the diagnostic industry.[1c]

The sulfopropyl group has historically been introduced by reaction of nucleophiles with commercially available and inexpensive, 1,3-propane sultone (**2**).[5a] Alkylation with 3-chloropropyl sulfonate has also been reported.[5b] Recently, Schmitt described sulfopropylation on compounds containing an allyl group using bisulfite via radical initiation.[6] Primary amines,[4] and sulfhydryl groups[3a,b] react readily with 1,3-propane sultone (1-4h) at room temperature but heterocyclic aromatic amines (pyridine, quinoline, acridine, etc.) require more drastic conditions, such as heating the substrate at >100 ^{0}C in neat 1,3-propane sultone for several hours. In this communication we describe a remarkably fast and convenient method for the introduction of sulfopropyl group into a variety of aromatic nitrogen containing heterocyclic compounds using 1,3-propane sultone (**2**) under microwave irradiation (Scheme 1).



1a-h **3a-h**

Scheme 1. Sulfopropylation of *N*-heterocyclic compounds (**1a-h**) under microwave irradiation

Typically, a mixture of heterocyclic compounds (**1a-h**) (1.0 mmol) and 1,3-propane sultone (**2**) (10.0 equiv.) in an open glass scintillation vial (25 mL) was irradiated for 15 to 60 sec in a domestic microwave oven. The crude reaction mixture was dissolved in DMF:water (1:1, 2.0 mL) and purified by preparative reverse phase HPLC [C18, MeCN:0.1% aqueous trifluoroacetic acid (10:90); 45 mL/min; 254 nm] followed by lyophilization.[9a] The results are summarized in the Table.

The reaction is general and affords *N*-sulfopropylated products (**3a-h**) in excellent yields (68-95%). We observed a dramatic increase in the rate of *N*-sulfopropylation and typically the process was complete in less than 1 minute. The reaction proceeds with minimal side reactions, and the desired product is easily purified by HPLC. The regioselectivity of sulfopropylation is demonstrated by the selective reaction on the aromatic nitrogen (entries **4**, **6**, **7**, and **8**). Neat propane sultone was found to be the reagent of choice for optimum yields.

In conclusion, we have developed a convenient method for *N*-sulfopropylation of heterocyclic compounds (**1a-h**) with 1,3-propane sultone using microwave irradiation. The method is fast, high yielding with minimum side reactions and can be effectively employed to a variety of complex *N*-heterocyclic systems.

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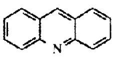
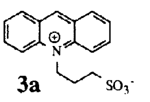
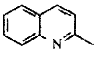
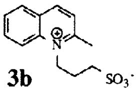
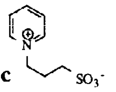
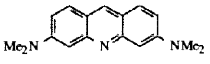
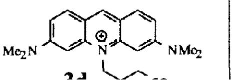
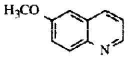
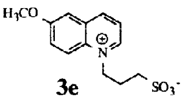
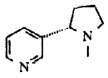
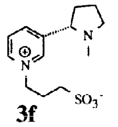
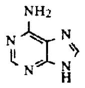
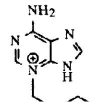
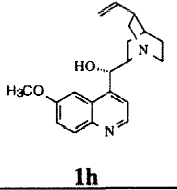
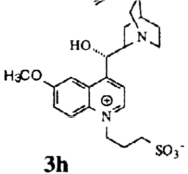
Table. Microwave Assisted Sulfopropylation of *N*-Heterocycles (**1a-1h**) using 1,3-Propane Sultone

Entry	Substrate (1a-h)	Product (3a-h)	Time /Power[a]	% Yield	Time/(%)Yield Ref.
1	 **1a**	 **3a**	1 min (M)	81	4h/70 ref. 5c
2	 **1b**	 **3b**	15 sec (H)	84	-
3	 **1c**	 **3c**	15 sec (H)	95	1h/100 ref. 8
4	 **1d**	 **3d**	15 sec (M)	68	1h/60 ref. 5c,9b, b
5	 **1e**	 **3e**	15 sec (H)	93	30 min/90 ref. 5c
6	 **1f**	 **3f**	15 sec (H)	92	ref. 9b
7	 **1g**	 **3g**	30 sec (H) in DMF	95	4h/47 ref. 7
8	 **1h**	 **3h**	15 sec (H)	75	ref. 9b

a) Panasonic Domestic Microwave Oven[Power H=high(900W), M=medium(55%H), L=low(10%H)]. b) yield was lower due to polysulfate ester formation.

References and Notes

1. a) Flanagan, J.H.; Khan, S.H.; Menchen, S.; Soper, S.A.; Hammer, R.P.; *Bioconjugate Chemistry* **1997**, *8*, 751. b) Wolfbeis, O.S.; Urbano, E. *J. Heterocyclic Chem.* **1982**, *19*, 841. c) Adamczyk, M.; Chen, Y.; Mattingly, P.G.; Pan, Y.; Rege, S. *J.Org. Chem.* **1998** (in press).
2. Carrea, G.; Ottolina, G.; Riva, S.; Danieli, B.; Lesma, G.; Palmisano, G. *Helv. Chim. Acta.* **1988**, *71*, 762.
3. a) Ruegg, U.T.; Rudinger, J. *Methods Enzymol.* **1977**, *47*, 116. b) Ruegg, U.T.; Rudinger, J. *Int. J. Pept. Protein Res.* **1974**, *6*, 447. c) Ikenoue, Y.; Saida, Y.; Kira, M.; Tomozaea, H.; Yahima, H.; Kobayashi, M. *J. Chem. Soc. Chem. Commun.* **1990**, 1694. d) Grosius, P.; Gallot, Y.C. *Russ..Acad. Sci.* C **1970**, *271*, 487.
4. Suga, K.; Miyashige, T.; Takada, K.; Watanabe, S.; Moriyama, M. *Aust. J. Chem.* **1968**, *21*, 2333.
5. a) Rohe, D. *Chem. Ind.* **1996**, *119*(9), 12. b) Mocanu, G.; Mihai, D.; Raileanu, D.; Carpov, A. *Cellu. Chem. Technol.* **1993**, *27*, 249. c) Wolbeis, O.S.; Urbano, E. *J. Heterocyclic Chem.* **1982**, *19*, 841.
6. Schmitt, K.D. *J.Org.Chem.* **1995**, *60*, 5474.
7. Carrea, G.; Ottolina, G.; Riva, S.; Danieli, B.; Lesma, G.; Palmisano, G. *Helv. Chem. Acta* **1988**, *71*, 762.
8. Helberger, J.H.; Manecke, G.; Heyden, R. *Justus Liebigs Ann. Chem* **1949**, *7*, 151.
9. a) 5-20% polysulfopropyl ester formation was evident. b) ES MS fragmentation study clearly established the substitution to be on the aromatic nitrogen.