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Selective Conversion of Alcohols into Alkyl Iodides Using a Thioiminium Salt

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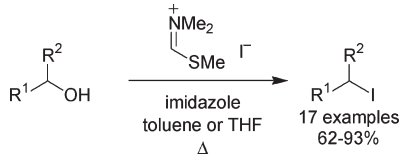


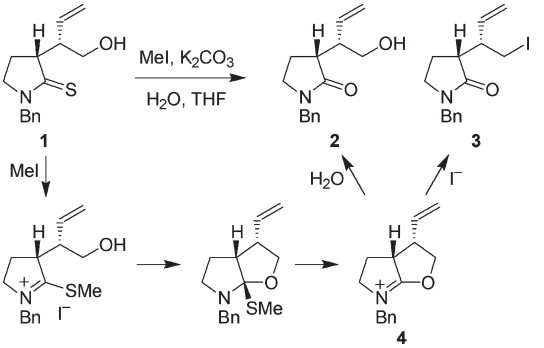
Treatment of a range of primary and secondary alcohols with $MeSCH{=}NMe_2^+\ I^-$ affords the corresponding alkyl iodides in excellent yield with straightforward purification. Selective formation of a primary iodide in the presence of a secondary alcohol can be achieved.

The direct conversion of alcohols to alkyl iodides is a transformation that is widely utilized in organic synthesis,[1] and there are a number of reagents which are used for this purpose. The most commonly used reagents on laboratory scale are based on phosphorus chemistry;[2] for example, PPh_3/I_2/imidazole,[3] PPh_3/NIS,[4] PPh_3/DEAD/MeI,[5] and $P(OPh)_3$/MeI.[6] These procedures generate stoichiometric quantities of triphenylphosphine oxide or diphenyl methylphosphonate, which can cause difficulties in product purification. Other procedures avoid the use of phosphines or phosphites—for example, the use of TMSI,[7] TMSCl/NaI,[8] HI,[9] P/I_2,[10] P_2I_4,[11] or of alkali metal iodides in conjunction with Lewis or Brønsted acids such as $CeCl_3$,[12] MsOH,[13] or $Al(HSO_4)_3$.[14]

In this note we describe a procedure for the efficient conversion of a wide range of primary and secondary alcohols to the corresponding iodides under essentially neutral conditions by treatment with the stable thioiminium salt *N*,*N*-dimethyl-*N*-(methylsulfanylmethylene)ammonium iodide. The byproducts of the reaction are readily removed from the desired alkyl iodides.

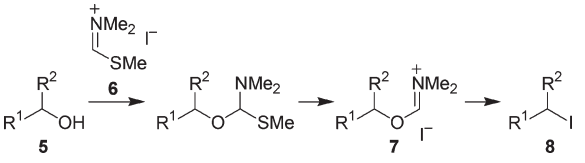
The origin of this process lies in our observation that the hydrolysis of thiolactam **1** using iodomethane in mild aqueous base gave, in addition to the expected lactam product **2**, a small amount of iodide **3** (Scheme 1).[15] This product was presumed to arise through initial *S*-methylation, cyclization of the pendant alcohol onto the activated thiocarbonyl group, and expulsion of methanethiol to give the bicyclic cation **4**. This cation could undergo either hydrolysis to the lactam **2** or S_N2 reaction with the iodide ion released from iodomethane to give alkyl iodide **3**.

SCHEME 1. Iodide Formation during Thiolactam Hydrolysis[15]



We reasoned that if the reaction of an alcohol **5** with a thioiminium salt such as **6** were to occur intermolecularly and in the absence of water, it should be possible to convert alcohols to iodides in this fashion (Scheme 2). Hence following initial nucleophilic attack of the alcohol on salt **6**, expulsion of MeSH would afford alkoxyiminium ion **7**; displacement of DMF would then lead to the iodide product **8**. We anticipated that the volatile nature of the byproducts, DMF and methanethiol, should make purification of **8** relatively straightforward.

SCHEME 2. Proposed Conversion of Alcohols to Iodides



(1) Härtinger, S. In *Science of Synthesis*; Georg Thieme Verlag: New York, 2007; Vol. 35, pp 589–672.
(2) Castro, B. R. *Org. React.* **1983**, *29*, 1–162.
(3) Garegg, P. J.; Samuelsson, B. *J. Chem. Soc., Chem. Commun.* **1979**, 978–980.
(4) Hanessian, S.; Ponpipom, M. M.; Lavallee, P. *Carbohydr. Res.* **1972**, *24*, 45–56.
(5) Loibner, H.; Zbiral, E. *Helv. Chim. Acta* **1976**, *59*, 2100–2113.
(6) (a) Landauer, S. R.; Rydon, H. N. *J. Chem. Soc.* **1953**, 2224–2234. (b) Rydon, H. N. *Org. Synth. Coll.* **1988**, *6*, 830–832.
(7) Jung, M. E.; Ornstein, P. L. *Tetrahedron Lett.* **1977**, 2659–2662.
(8) (a) Olah, G. A.; Narang, S. C.; Gupta, B. G. B.; Malhotra, R. *J. Org. Chem.* **1979**, *44*, 1247–1251. (b) Morita, T.; Yoshida, S.; Okamoto, Y.; Sakurai, H. *Synthesis* **1979**, 379.
(9) Norris, J. F. *Am. Chem. J.* **1907**, *38*, 627–642.
(10) Hartman, W. W.; Byers, J. R.; Dickey, J. B. *Org. Synth. Coll.* **1943**, *2*, 322.
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(12) Di Deo, M.; Marcantoni, E.; Torregiani, E.; Bartoli, G.; Bellucci, M. C.; Bosco, M.; Sambri, L. *J. Org. Chem.* **2000**, *65*, 2830–2833.
(13) Kamal, A.; Ramesh, G.; Laxman, N. *Synth. Commun.* **2001**, *31*, 827–833.
(14) Tajik, H.; Shirini, F.; Zolfigol, M. A.; Samimi, F. *Synth. Commun.* **2006**, *36*, 91–95.
(15) Mortimer, A. J. P.; Pang, P. S.; Aliev, A. E.; Tocher, D. A.; Porter, M. J. *Org. Biomol. Chem.* **2008**, *6*, 2941–2951.

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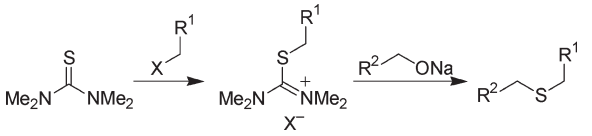
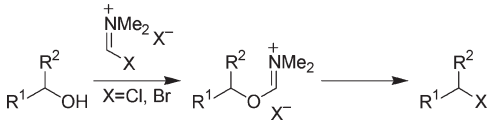
The use of *S*-alkylated thiocarbonyl compounds for the activation of alcohols has some precedent; Kajigaeshi et al. showed that unsymmetrical sulfides could be prepared by successive reaction of *N*,*N*,*N*′,*N*′-tetramethylthiourea with an alkyl halide and an alkoxide (Scheme 3).[16] In this case, the *O*-alkyluronium salt (cf. **7**) reacts with the liberated thiolate rather than the halide counterion.

SCHEME 3. Preparation of Unsymmetrical Sulfides[16]



Further related precedent comes from the reaction of alcohols with haloiminium halides (Vilsmeier reagents) to give alkyl halides (Scheme 4).[17] While useful for the preparation of chlorides and bromides, this reaction is not amenable to the preparation of alkyl iodides.

SCHEME 4. Formation of Haloalkanes with Haloiminium Salts[17]



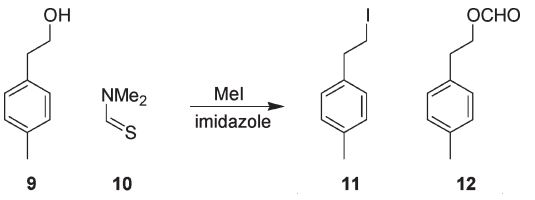
Our initial iodination studies utilized 2-(4-methylphenyl)-ethanol (**9**) as the alcohol substrate. Treatment of a THF solution of this alcohol and *N*,*N*-dimethylthioformamide (**10**, 2 equiv) with iodomethane (4 equiv) gave the expected iodide **11**, together with formate ester **12**. Addition of imidazole was found to accelerate the reaction (Table 1, entry 1).

A number of different solvents were screened for the iodination reaction (Table 1), with the best results being obtained in THF, toluene, and acetonitrile.

The formate byproduct **12** was formed to varying extents in all reactions. This compound was assumed to arise through hydrolysis of the intermediate alkoxyiminium ion **7** by adventitious water,[17b,18] and so various drying agents were added (molecular sieves, $MgSO_4$, MgO) but none was effective in preventing the formation of **12**.

We next considered the possibility of carrying out the iodination with a preformed iminium salt rather than a mixture of thioamide and iodomethane. *N*,*N*-Dimethyl-*N*-(methylsulfanylmethylene)ammonium iodide (**6**) was prepared by stirring *N*,*N*-dimethylthioformamide with iodomethane in diethyl ether and filtering off the crystalline product.[19]

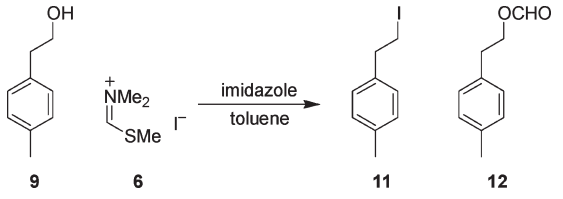
TABLE 1. Screening of Solvents for Formation of a Primary Iodide[a]



	solvent	conversion/ %[b]	ratio **11**:**12**[b]
1	THF	100	11:1
2	CH_2Cl_2	100	5.9:1
3	Et_2O	39	1:3.6
4	toluene	92	11:1
5	MeCN	96	10.5:1
6	DMF[c]	5	0:1

[a]Conditions: 2 equiv **10**, 4 equiv MeI, 2 equiv imidazole, reflux, 4 h. [b]Determined from integration of crude ^{1}H NMR spectra. [c]Reaction conducted at 120 °C.

TABLE 2. Optimization of Conditions for Iodide Formation



	equiv **6**	equiv imidazole	temp /°C	time /h	conversion /%[a]	ratio **11**:**12**[a]
1	1.5	1	85	1.5	100	12.2:1
2	1.5	0.5	85	1.5	100	13:1
3	1.5	0.25	85	3	100	16:1
4	1.1	0.5	85	4	90	8:1
5	2	0.5	85	1.25	100	13:1
6	3	0	85	3.5	24	50:1
7	1.5	1	20	18	44	1:1
8	1.5	0.5	20	18	25	0:1
9	1.5	0.5	85[b]	1.5	100	24:1

[a]Determined from integration of crude ^{1}H NMR spectra. [b]The solution of alcohol was heated to 85 °C prior to addition of **6** and imidazole.

Pleasingly, salt **6** proved effective in converting alcohol **9** to iodide **11**, and optimization of the reaction conditions was carried out using this reagent in toluene (Table 2).

Initially, 1.5 equiv of salt **6** and 1 equiv of imidazole were added to a solution of alcohol **9** in toluene and the mixture heated to 85 °C (entry 1); under these conditions, reaction was complete in 90 min, with a good ratio of iodide **11** to formate **12**. Reduction of the imidazole loading to 0.5 equiv (entry 2) had no detrimental effects, while with 0.25 equiv (entry 3), the reaction was slowed slightly.

Use of less than 1.5 equiv of salt **6** (entry 4) resulted in slower conversion and an inferior ratio of iodide to formate, while use of more than this amount (entry 5) did not markedly improve the reaction rate or product ratio. Omission of the imidazole, even with a 3-fold excess of salt (entry 6), led to very slow reaction.

When the reaction was carried out at room temperature (entries 7 and 8), conversion was slow and a large amount of the undesired formate **12** was obtained.

(16) Fujisaki, S.; Fujiwara, I.; Norisue, Y.; Kajigaeshi, S. *Bull. Chem. Soc. Jpn.* **1985**, *58*, 2429–2430.

(17) (a) Eilingsfeld, H.; Seefelder, M.; Weidinger, H. *Angew. Chem.* **1960**, *72*, 836–845. (b) Hanessian, S.; Plessas, N. R. *Chem. Commun.* **1967**, 1152–1155. (c) Dods, R. F.; Roth, J. S. *Tetrahedron Lett.* **1969**, 165–168. (d) Hepburn, D. R.; Hudson, H. R. *J. Chem. Soc., Perkin Trans. 1* **1976**, 754–757.

(18) (a) Johnson, R. A.; Herr, M. E. *J. Org. Chem.* **1972**, *37*, 310–312. (b) Boeckman, R. K.; Ganem, B. *Tetrahedron Lett.* **1974**, 913–916.

(19) (a) Singh, H.; Batra, M. S.; Singh, P. *Indian J. Chem., Sect. B: Org. Chem. Incl. Med. Chem.* **1984**, *23*, 1176–1180. (b) Berrée, F.; Malvaut, Y.; Marchand, E.; Morel, G. *J. Org. Chem.* **1993**, *58*, 6022–6029. (c) Gompper, R.; Elser, W. *Org. Synth. Coll.* **1973**, *5*, 780–784.

Given the increased preponderance of the formate byproduct in the reactions conducted at room temperature, we considered that some of the formate in earlier experiments may have been produced while the reaction mixture was being heated to 85 °C. Gratifyingly, heating the solution of alcohol to 85 °C before addition of the salt **6** and imidazole (entry 9) further increased the ratio of iodide **11** and formate **12** to 24:1.

Using these optimized reaction conditions and the equivalent reaction in THF, a study of the scope and functional group compatibility of the conversion was next carried out; these results are summarized in Table 3.[20]

Primary alcohols were converted in excellent yield to the corresponding iodides (Table 3, entries 1−9). Many common functional and protecting groups including nitro groups (entry 2), THP ethers (entry 3), silyl ethers (entry 4), esters (entry 5), *tert*-butyl carbamates (entry 6), nitriles, tertiary aromatic amines (entry 7), alkenes (entry 8), and acetonides (entry 9) were found to be compatible with the reaction conditions.

Conversion of diacetonegalactose to the corresponding iodide (entry 9) was slightly lower-yielding than the preceding reactions, with the formate ester of the original alcohol being the main byproduct. A longer reaction time resulted in a slightly improved yield. With a neopentylic primary alcohol (entry 10), no iodide was formed, with formylation being the major process observed.

Conversion of secondary alcohols to the corresponding iodides was also possible, but extended reaction times or higher quantities of reagents were required. Nevertheless, secondary iodides could be obtained in good yields (entries 11−13). However, when diacetone glucose was subjected to the reaction conditions (entry 14), no iodide was formed and only small quantities of the formate ester could be isolated. Tertiary alcohols proved inert to the reaction conditions.

Given the observed difference in reaction rate between primary and secondary alcohols, two primary−secondary diols were subjected to the iodination conditions to find out whether selective reaction was possible. A 1,2-diol (entry 15) gave a moderate yield of the iodoalcohol resulting from preferential reaction of the primary alcohol, but partial dideoxygenation to give the corresponding alkene was also observed. A 1,3-diol (entry 16) underwent selective and clean conversion to a primary iodide, with the secondary alcohol remaining unreacted.

Two allylic alcohols were investigated (entries 17, 18). Use of the standard conditions led to consumption of the starting materials, but the desired iodide was not obtained cleanly. However, by lowering the reaction temperature to 55 °C and decreasing the reaction concentration, allylic iodides could be obtained in good yield.

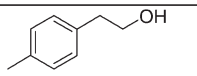
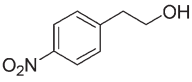
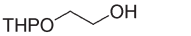
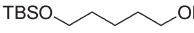
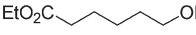
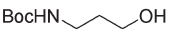
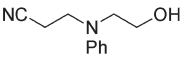
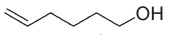
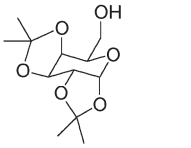
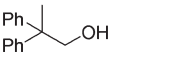
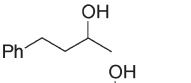
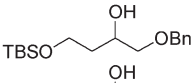
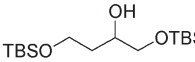
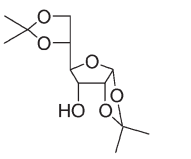
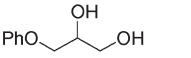
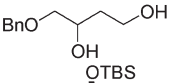
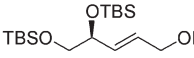
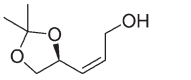
The stereochemical course of the reaction was studied using (*R*)-octan-2-ol (**13**) as a substrate (Scheme 5). Samples were withdrawn during the course of reactions and analyzed by ^{1}H NMR and chiral GC (Figure 1).

After 30 min in toluene at 85 °C, alcohol **13** had undergone 27% conversion to iodide **14**; the enantiomeric excess of this iodide was found to be 79%. As the reaction proceeded, the enantiomeric purity of the product dropped, and after 8 h, the iodide could be isolated in 73% yield but with only 11% enantiomeric excess.

Similar results were obtained in THF at reflux, but with a higher rate of formation of **14** and a more rapid deterioration of its enantiomeric excess. After 8 h, racemic **14** was obtained in 78% yield.

Conversely, carrying out the reaction in toluene at 55 °C led to slower conversion but also to a diminished

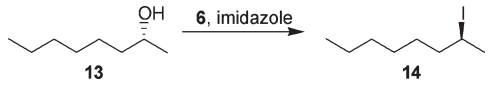
TABLE 3. Conversion of a Range of Alcohols to Iodides with Salt 6

	Alcohol	Toluene[a] Time / min	Toluene[a] Yield / %[c]	THF[b] Time / min	THF[b] Yield / %[c]
1		90	92	60	90
2		90	84	90	85
3		50	88	50	82
4		210	90	150	84
5		90	93	90	91
6		120	82	120	87
7		80	91	90	87
8		80	81	60	83
9		1080	70	1080	63
10		150	–	120	–
11		210	86[d]	150	87[d]
12		2880	75[e]	2880	70[e]
13		4320	60 (80)[e]	2880	76[e]
14		360	–[f]	420	–[g]
15		180	62[h]	120	59[h]
16		60	82[i]	60	83[i]
17		2880	64 (84)[j]	2880	61 (77)[j]
18		150	71[j]	240	41[j]

[a]Conditions: 0.20−0.25 M substrate, 1.5 equiv **6**, 0.5 equiv imidazole, toluene, 85 °C. [b]Conditions: 0.20−0.25 M substrate, 1.5 equiv **6**, 0.5 equiv imidazole, THF, reflux. [c]Isolated yield following chromatography; yields in parentheses are based on recovered starting material. [d]Imidazole (1.0 equiv) used. [e]**6** (2.5 equiv), 1.0 equiv imidazole used. [f]Formate isolated in 10% yield. [g]Formate isolated in 16% yield. [h]Yield is of 1-phenoxy-3-iodopropan-2-ol; phenyl allyl ether formed as the major byproduct. [i]Yield is of 1-benzyloxy-4-iodobutan-2-ol. [j]Reaction conducted at 55 °C with a substrate concentration of 0.14 M.

(20) While acetonitrile had been successfully used in the conversion of **9** to **11**, the substrate scope of the iodination in this solvent proved to be less broad than in either THF or toluene.

SCHEME 5. Conversion of (*R*)-Octan-2-ol to (*S*)-2-Iodooctane



degradation of the enantiomeric purity. In this case, the enantiomeric excess of iodide **14** after 8 h was 81%.

The decrease in enantiomeric excess of **14** from a high starting value over the course of these reactions suggests that the initial conversion of **13** to **14** occurs, as expected, with inversion of configuration; however, the presence of excess iodide ions results in further S_N2 reactions which interconvert **14** and its enantiomer, racemizing the product.[21]

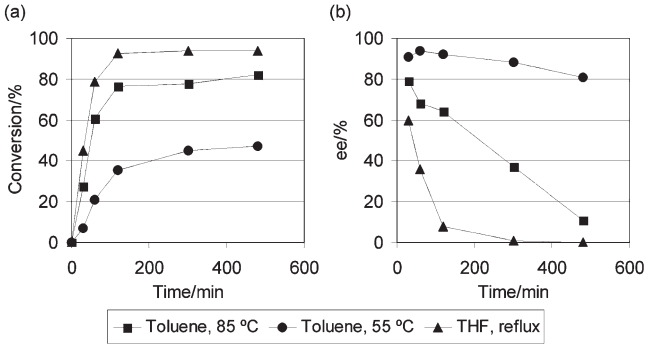


FIGURE 1. (a) Percentage conversion to **14** (by ^{1}H NMR) and (b) enantiomeric excess of **14** (by chiral GC) in the reaction of alcohol **13** with salt **6**.

Purification of the iodide products is very straightforward; the crude reaction mixture is concentrated in vacuo, removing the solvent, methanethiol, and most of the DMF to give an iodide containing traces of imidazole and *N*,*N*-dimethylthioformamide. Both of these polar impurities are retained strongly on silica or alumina, and the product is easily purified by column chromatography.

The salt **6** is a stable reagent which can be stored for several months without degradation. Carrying out the reaction of **9** in toluene with a sample of **6**, which had been stored at −25 °C for 18 weeks, gave a 90% yield of iodide **11**.

(21) Hughes, E. D.; Juliusberger, F.; Masterman, S.; Topley, B.; Weiss, J. *J. Chem. Soc.* **1935**, 1525–1529.

In conclusion, we have developed a stable and readily prepared reagent which allows the conversion of a range of primary and secondary alcohols to the corresponding alkyl iodides in good yield. Primary alcohols react more rapidly than secondary, and selective conversions can be achieved. Many common functional groups, including acid-sensitive moieties, are tolerated, and the products require minimal purification.

Experimental Section

***N*,*N*-Dimethyl-*N*-(methylsulfanylmethylene)ammonium Iodide (6).** To a stirred solution of *N*,*N*-dimethylthioformamide (3.00 g, 33.7 mmol) in diethyl ether (70 mL) was added iodomethane (5.26 g, 37.1 mmol). The mixture was stirred at room temperature for 18 h, and the solid product collected by filtration under argon. The solid was washed with cold diethyl ether (2 × 25 mL) and dried under vacuum to afford salt **6** (7.47 g, 96%) as a white solid, which was used without further purification; mp 131−132 °C. ν_{max}/cm^{-1} (neat) 2983, 1639, 1619, 1442, 1408. ^{1}H NMR ($CDCl_3$, 600 MHz) δ 3.16 (3H, s), 3.40 (3H, s), 3.90 (3H, s), 11.14 (1H, s). ^{13}C NMR ($CDCl_3$, 150 MHz) δ 16.6, 42.7, 48.9, 183.5. HRMS (CI^+) found 104.0537, $C_4H_{10}NS$ requires 104.0534.

Typical Procedure for Iodination of Alcohols; 1-Iodo-2-(4-methylphenyl)ethane (11). A solution of 2-(4-methylphenyl)-ethanol (**9**, 102 mg, 0.75 mmol) in toluene (3.5 mL) was heated to 85 °C. *N*,*N*-Dimethyl-*N*-(methylsulfanylmethylene)ammonium iodide (**6**, 260 mg, 1.12 mmol) and imidazole (25 mg, 0.37 mmol) were added and the mixture stirred at 85 °C for 90 min. After cooling to room temperature, the reaction mixture was concentrated in vacuo to afford the crude product. Purification by flash chromatography (SiO_2; petrol) afforded iodide **11** as a colorless oil (170 mg, 92%). ν_{max}/cm^{-1} ($CHCl_3$ cast) 3019, 2920, 1513. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.35 (3H, s), 3.16 (2H, t, *J* 8.0 Hz), 3.36 (2H, t, *J* 8.0 Hz), 7.11 (2H, d, *J* 8.0 Hz), 7.16 (2H, d, *J* 8.0 Hz). ^{13}C NMR ($CDCl_3$, 125 MHz) δ 6.0, 21.2, 40.1, 128.3, 129.4, 136.6, 137.7. HRMS (EI) found 245.9897, $C_9H_{11}I$ requires 245.9900.

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Supporting Information Available: Characterization data and ^{1}H and ^{13}C NMR spectra for all synthesized compounds. This material is available free of charge via the Internet at http://pubs.acs.org