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Tetrahedron Letters 49 (2008) 2638–2641
Tetrahedron Letters

Simple synthesis of fresh alkyl iodides using alcohols and hydriodic acid

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Received 26 April 2007; revised 14 February 2008; accepted 15 February 2008
Available online 7 March 2008

Abstract

A simple synthesis of fresh alkyl iodides using alcohols and hydriodic acid (HI) is reported. The alkyl iodides were obtained in quick and easy work-up with good to excellent yields (66–94%) and very high purities (97–99%). Freshly prepared iodomethane and 1-iodobutane were applied to synthesize biologically relevant 3,7-dimethyladenine and 9-butyladenine, which were characterized thoroughly using 1D and 2D NMR, individually.

Keywords: Alcohols; Hydriodic acid; Hydrogen bromide; Hydriodination; Hydrobromination; Alkyl iodides; Alkyl bromides

Alkyl halides are very useful reagents in organic chemistry, molecular biology, and chemical biology (Fig. 1).[1–4] The alkyl halides have been applied to the synthesis of effective drugs to treat many deadly human diseases, such as cancer,[5,6] HIV,[7] diabetes,[8] and arthritis.[9] They are also useful in nano material fabrication and nanotechnologies.[10] To study how alkylators affect human health and diseases, the alkyl iodides are widely used to the alkylation of DNA for crystallographic study of DNA repair protein AlkB[1,11] and structural study of DNA repair protein 3-methyladenine DNA glycosylase I (TAG) using NMR.[12] Recently, the alkyl iodides have been used to alkylate proteins directly,[13,14] RNA related compounds[15] and even live cells.[16]

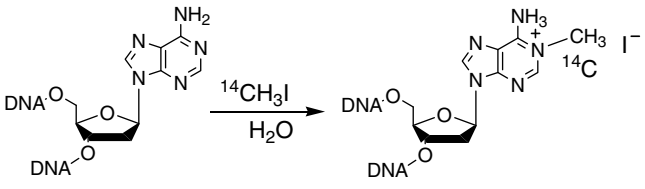

Fig. 1. Synthesis of methylated DNA using $^{14}CH_3I$.[1]

However, most of alkyl iodides are not very stable in room temperature or even at 4 °C.[17–19] They decompose automatically and quickly, resulting in dark color and impurities, which could affect the confidence of drawing conclusions in biological studies, especially in cell death and phenotype research. Fresh and pure alkyl iodides are needed in organic chemistry, medicinal chemistry, drug discovery, and molecular biology.

Alkyl iodides can be synthesized in many ways. A traditional method is to use the reactions of alcohols with phosphorus triiodide to make alkyl iodides.[20] However, the reactions generate toxic H_3PO_3. Another method is to apply the cleavages of dialkyl ethers using hydriodic acid, however, many ethers are not readily available.[21] Some modern methods to synthesize alkyl iodides include the reaction of alcohols with cesium iodide in the presence of *p*-toluenesulfonic acid,[22] nucleophilic substitution of alkyl chlorides with an excess of sodium iodide,[23] rapid reaction of organoboranes with iodine under the presence of a base,[24] and conversion of alcohols to alkyl halides using halide-based ionic liquids.[25] However, none of the syntheses are cost effective or convenient.

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0040-4039/$ - see front matter © 2008 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetlet.2008.02.106

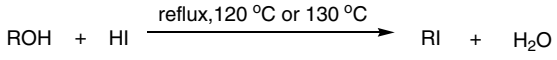
Hydriodic acid and hydrogen bromide can be reusable, and iodine and bromine can also be recycled from the acids.[26–28] Thus, the application of hydriodic acid and hydrogen bromide in the synthesis of alkyl iodides and alkyl bromides should be environmentally benign. The hydriodic acid had been used to synthesize isotope labeled iodomethane and iodoethane.[29,30] However, the syntheses either took a long time to complete or resulted in low yields. Surprisingly, there is no report on the synthesis of longer aliphatic chain alkyl iodides or benzyl iodide using the hydriodic acid and the corresponding alcohols.

Alkyl halides should be synthesized easily from alcohols and hydrogen halides by reflux. However, we found that the reflux of 1-butanol (2.34 g, 31.5 mmol) with 48% hydrogen bromide (7 mL) for 4 h on a 120 °C oil bath only gave low yield of 1-bromobutane (54%) and moderate purity (93%). The yield of 1-bromobutane was improved to 82% with 90% purity by adding additional sulfuric acid (98%, 1 mL). Interestingly, we found that 1-iodobutane could be directly synthesized using 1-butanol and hydriodic acid (HI, 57%) by reflux without adding an additional acid in 80% yield with 98% purity (Scheme 1 and Table 1).

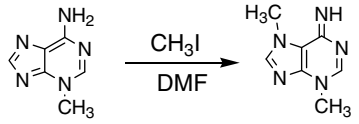
The methodology for the synthesis of 1-iodobutane was also applied to the synthesis of other alkyl iodides (Table 1). Iodomethane and iodoethane were synthesized in 76% and 72% yields with 99% purities individually using corresponding methanol, ethanol, and hydriodic acid. They were collected by distillation to flasks on an ice-water bath for 2 h after mixing of the alcohol with hydriodic acid. The reaction time was only about one fifth of that reported for the preparation of ^{13}C-iodomethane using ^{13}C-methanol and hydriodic acid.[29] Furthermore, besides 1-butanol, methanol and ethanol, 1-propanol, 1-pentanol, and benzyl alcohol were also found to be miscible with 57% hydriodic acid. Their corresponding alkyl iodides, 1-iodopropane, 1-iodopentane, and benzyl iodide were also synthesized in good to excellent yields (66%, 83%, and 93%, respectively) with very high purities (99%, 98%, and 99%, respectively).

However, we found that the alcohols with longer chains (C6–C8) were immiscible with 57% HI. As a result, the reflux of the three alcohols with hydriodic acid only gave moderate to good yields of the corresponding alkyl iodides (72%, 75%, and 69%, individually) with low purities (82%, 84%, and 77%, individually) (Table 1). To improve the yields and purities of the alkyl iodides, we added H_3PO_4 to the reaction mixtures during the hydriodination of these alcohols. The oil bath temperature was raised to 130 °C. As a result, all of the three alkyl iodides were then obtained in excellent yields (90%, 94%, and 92%, individually) with very high purities (99%, 98%, and 97%, individually).

Furthermore, the freshly prepared iodomethane and 1-iodobutane were used to make biologically important known compounds 3,7-dimethyladenine (Scheme 2) and 9-butyladenine (Scheme 3), respectively. The synthesis of 3,7-dimethyladenine was carried out in DMF at room temperature, by methylating DNA base 3-methyladenine

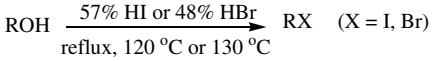


Scheme 1. Synthesis of alkyl iodides using alcohols and hydriodic acid.



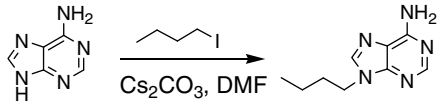
Scheme 2. Synthesis of 3,7-dimethyladenine using freshly made iodomethane.

Table 1
Simple synthesis of fresh alkyl halides using alcohols and HI



Entry	R	X	Conditions	Oil bath temp (°C)	Yield[a] (%)	Purity[b] (%)
1	CH_3	I	Distillation, 2 h	120	76	99
2	CH_3CH_2	I	Distillation, 2 h	120	72	99
3	$CH_3(CH_2)_2$	I	Reflux, 4 h	120	66	99
4	$CH_3(CH_2)_3$	I	Reflux, 4 h	120	80	98
5	$CH_3(CH_2)_4$	I	Reflux, 4 h	120	83	98
6	$CH_3(CH_2)_5$	I	Reflux, 4 h	120	72	82
7	$CH_3(CH_2)_5$	I	Reflux, 4 h (H_3PO_4)	130	90	99
8	$CH_3(CH_2)_6$	I	Reflux, 4 h	120	75	84
9	$CH_3(CH_2)_6$	I	Reflux, 6 h (H_3PO_4)	130	94	98
10	$CH_3(CH_2)_7$	I	Reflux, 4 h	120	69	77
11	$CH_3(CH_2)_7$	I	Reflux, 8 h (H_3PO_4)	130	92	97
12	$C_6H_5CH_2$	I	Reflux, 4 h	120	93	99
13	$CH_3(CH_2)_3$	Br	Reflux, 4 h	120	54	93
14	$CH_3(CH_2)_3$	Br	Reflux, 4 h (H_2SO_4)	120	82	99
15	$C_6H_5CH_2$	Br	Reflux, 4 h	120	92	99

[a] Isolated yield.
[b] Purity based on gas chromatography.



Scheme 3. Synthesis of 9-butyladenine using freshly made 1-iodobutane.

without adding any additional base. The 3,7-dimethyladenine was isolated by using HPLC and C-18 reverse phase column in 60% yield. The 9-butyladenine was synthesized by alkylating of a DNA base adenine in DMF using 1-iodobutane in the presence of cesium carbonate. The purification of the 9-butyladenine was achieved by double recrystallization using toluene then 10% ethanol–water solution, resulting in a final yield of 51%. Without the second re-crystallization in ethanol–water, the purity of 9-butyladenine was never good. Both compounds were characterized using 1D NMR and 2D NMR (Figs. 2 and 3 for 3,7-dimethyladenine and 9-butyladenine, respectively). The 3,7-dimethyladenine will continually be used in the study of the DNA repair proteins, such as AlkB[1,11] and TAG.[12] The 9-butyladenine will be used to inhibit enzymes, such as kinase p38 gamma.[31] The biological investigations using 3,7-dimethyladenine and 9-butyladenine are on the way.

In summary, a novel and simple method for the preparation of fresh alkyl halides is reported from the readily available alcohols and hydriodic acid. This method should find wide application in organic synthesis and drug discovery, using the alkyl iodides to make a variety of chemicals as drugs to treat many deadly human diseases. The alkyl iodides will also be very useful in chemical, biology, and molecular biology studies.

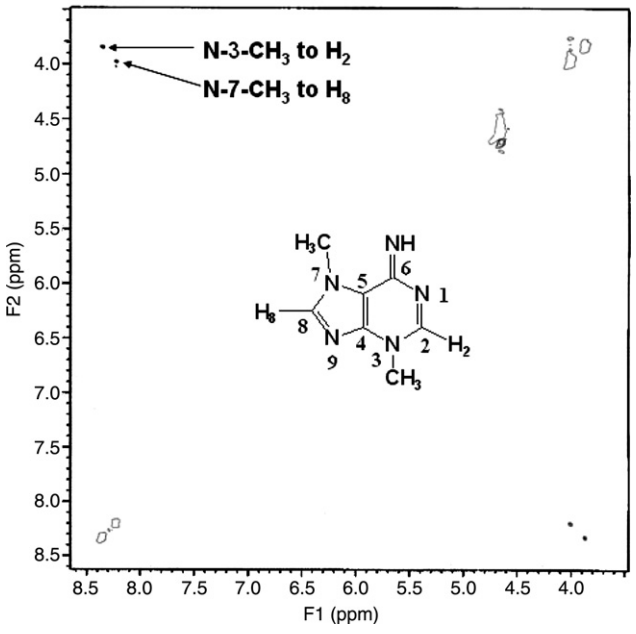


Fig. 2. NMR (400 MHz) NOE spectrum of 3,7-dimethyladenine and typical hydrogen to hydrogen correlations.

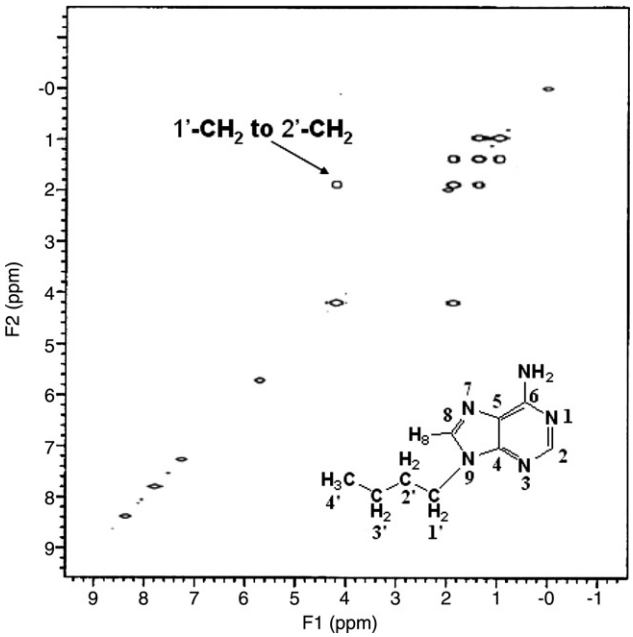


Fig. 3. NMR (400 MHz) COSY spectrum of 9-butyladenine and a typical hydrogen to hydrogen correlation.

Acknowledgments

This research is supported by the Office of Research and Sponsored Programs and Department of Chemistry at East Tennessee State University. We also thank Dr. Mohseni for assistance in gas chromatography, and Mrs. Susan Campbell for error-proof reading.

Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2008.02.106.

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