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of Reliable Methods
for the Preparation
of Organic Compounds

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The procedures in *Organic Syntheses* are intended for use only by persons with proper training in experimental organic chemistry. All hazardous materials should be handled using the standard procedures for work with chemicals described in references such as "Prudent Practices in the Laboratory" (The National Academies Press, Washington, D.C., 2011; the full text can be accessed free of charge at http://www.nap.edu/catalog.php?record_id=12654). All chemical waste should be disposed of in accordance with local regulations. For general guidelines for the management of chemical waste, see Chapter 8 of Prudent Practices.

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September 2014: The paragraphs above replace the section "Handling and Disposal of Hazardous Chemicals" in the originally published version of this article. The statements above do not supersede any specific hazard caution notes and safety instructions included in the procedure.

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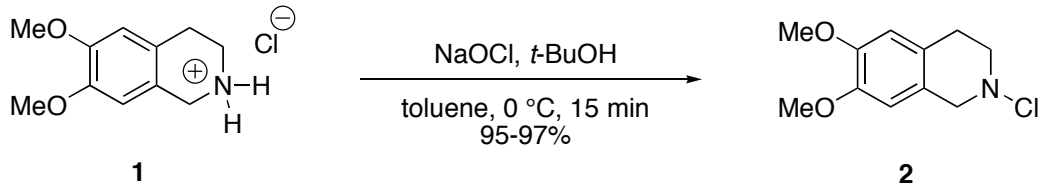
A PRACTICAL AND SCALABLE SYNTHESIS OF *N*-HALO COMPOUNDS: 2-CHLORO-6,7-DIMETHOXY-1,2,3,4-TETRAHYDROISOQUINOLINE



1 **2**

Submitted by Yong-Li Zhong[1] and Paul G. Bulger.
Checked by Stephen G. Newman and Mark Lautens.

1. Procedure

2-Chloro-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline (**2**). A 250-mL, three-necked, round-bottomed flask is equipped with an overhead stirrer, an addition funnel that is fitted with a tap adaptor connected to a nitrogen line, and a rubber septum through which a digital thermometer probe is inserted. The septum is temporarily removed and the apparatus is purged with nitrogen for 5 min and then the flask is charged with 6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline hydrochloride **1** (5.16 g, 21.8 mmol, 1.0 equiv) (Notes 1 and 2), *tert*-butanol (2.11 mL, 21.8 mmol, 1.0 equiv) (Note 3), water (15 mL) (Note 4), and toluene (40 mL) (Note 5) at room temperature. The septum is replaced and the mixture is stirred at 120 rpm, and the resulting biphasic solution is cooled to −5 °C (internal temperature) in an ice/salt bath over which time the aqueous layer freezes to became a white slurry in the organic layer. The addition funnel is charged with 5% aqueous sodium hypochlorite (30.9 mL, 25.1 mmol, 1.15 equiv, Note 6), which is then added dropwise over 30 min to the reaction mixture, maintaining the internal temperature between −5 and 0 °C. Once the addition is complete, stirring is continued at this temperature for a further 15 min (Note 7). Once the mixture reaches >15 °C, it is transferred to a 125 mL separatory funnel (washing with 2 × 10 mL of toluene). The layers are separated and the lower, aqueous layer is discarded. The colorless organic layer is washed with water (1 × 15 mL), and then with brine (1 × 15 mL) (Note 8). The organic layer is concentrated by rotary evaporation (20 mmHg, keeping the bath temperature below 30 °C) to a volume of approximately 12 mL (Note 9). A stir bar is added, and to the stirred toluene

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solution is then added *n*-heptane (40 mL) (Note 10) dropwise *via* an addition funnel over 20 min at room temperature, and the resulting white slurry is then cooled to 0 °C in an ice bath and stirred at that temperature for a further 3 h. The crystalline product is then collected by filtration through a 60-mL fritted-glass funnel of medium porosity. The wet solid is washed with *n*-heptane (2 × 10 mL) and then dried under vacuum with a nitrogen sweep (Note 11) for 1 h to give 2-chloro-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline **2** (4.70–4.83 g, 95–97%) (Notes 12, 13, and 14) as a white powder (Note 15).

2. Notes

1. 6,7-Dimethoxy-1,2,3,4-tetrahydroisoquinoline hydrochloride **1** (97%) was purchased from Sigma-Aldrich, Inc. and used as received.

2. If the starting material is an amide or a neutral amine, then the addition of one equivalent of acetic acid to the reaction is also required.

3. *tert*-Butanol (anhydrous, ≥ 99.5%) was purchased from Sigma-Aldrich, Inc. and used as received (submitters used 99+% grade from Sigma-Aldrich, Inc.).

4. Distilled water was used (submitters used deionized water).

5. Toluene was purchased from ACP Chemicals, Canada and used as received (submitters used 99% grade from Sigma-Aldrich, Inc.).

6. 5% Aqueous sodium hypochlorite (bleach) was purchased from Acros Organics Ltd. and used as received.

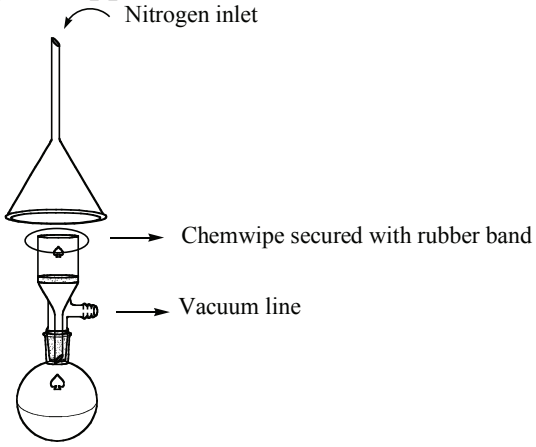
7. The progress of the reaction was followed by TLC analysis on silica gel with visualization under UV (254 nm) and with a ceric ammonium molybdate stain. Using an eluent comprising 10% methanol in dichloromethane, product **2** has R_f = 0.87, while the starting amine **1** has R_f = 0.22. Alternatively, the reaction was monitored by reverse-phase HPLC employing the following conditions: Zorbax Eclipse Plus C18 Rapid Resolution HT column (4.6 × 50 mm, 1.8 μm particle size, Agilent part number: 253583-0191); column temperature 25 °C; flow rate: 1.5 mL/min; linear gradient of 10:90 to 95:5 acetonitrile:0.1% v/v aqueous H_3PO_4 in 5 min, then hold at 95:5 for 1 min, then back to 10:90 in 0.1 min, then hold at 10:90 for 1.9 min; UV detection at 210 nm. Retention times for compounds **1** and **2** are 0.83 and 4.53 min, respectively.

8. At this stage the organic layer may be dried using sodium sulfate (2 g) for 0.5 h if necessary.

9. The product may begin to crystallize prior to the addition of heptane, depending upon the exact volume of the toluene solution and ambient temperature.

10. *n*-Heptane was purchased from ACP Chemicals, Canada and used as received (submitters used 99% grade from Sigma-Aldrich, Inc.).

11. The product is dried for 1 h under house vacuum (20 mmHg) with a nitrogen sweep, using the apparatus illustrated below:



12. Physical properties and spectroscopic data for **2** are as follows: white powder; mp >76 °C (dec.); IR (film): 2935, 2830, 1610, 1520, 1465, 1360, 1260, 1220, 1120 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ: 2.96 (t, J = 6.0 Hz, 2 H), 3.43 (t, J = 6.0 Hz, 2 H), 3.84 (s, 3 H), 3.85 (s, 3 H), 4.24 (s, 2 H), 6.47 (s, 1 H), 6.59 (s, 1 H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 28.1, 55.9 (2 peaks), 59.2, 63.4, 109.1, 111.1, 124.1, 125.1, 147.6, 148.1; HRMS (ESI) *m/z* calcd. for $C_{11}H_{15}ClNO_2$ $[M+H]^+$ 228.0785; found 228.0780; Anal. calcd. for $C_{11}H_{14}ClNO_2$: C, 58.05; H, 6.20; N, 6.15; found: C, 58.05; H, 6.29; N, 6.20.

13. During melting-point analysis, the solid product **2** decomposed rapidly at 76 °C to give a brown oil. Differential scanning calorimetry (DSC) studies suggested that the product was stable at temperatures below 61 °C. Handling and manipulation of this, and other, *N*-halo compounds at or below 30 °C is therefore recommended.

14. The crystalline product **2** gave negative results in drop-weight tests, indicating that the material is not shock-sensitive.

15. The white product slowly colorized to pale yellow upon standing at room temperature. However, the product was stable at room temperature for several weeks without noticeable degradation.

Safety and Waste Disposal Information

All hazardous materials should be handled and disposed of in accordance with "Prudent Practices in the Laboratory"; National Academy Press; Washington, DC, 1995.

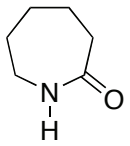
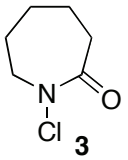
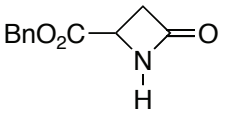
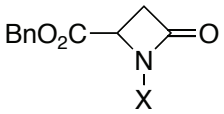
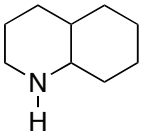
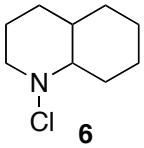
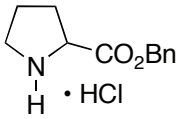
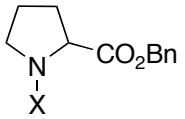
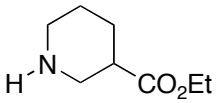
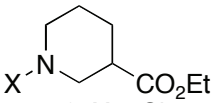
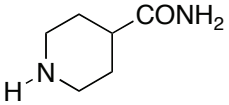
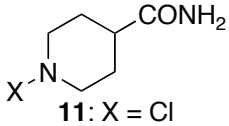
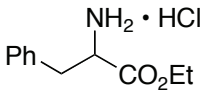
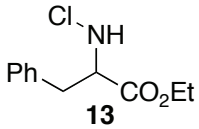
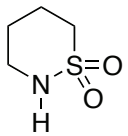
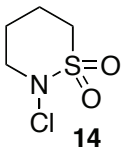
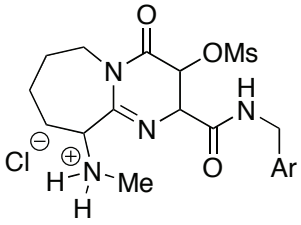
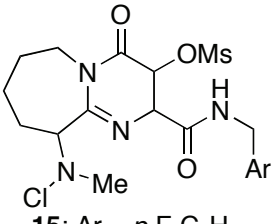
3. Discussion

N-Halo compounds are versatile reagents in synthesis. For many organic chemists, experience with *N*-chloro or *N*-bromo derivatives is limited to the use of the halogenating agents *N*-chlorosuccinimide (NCS) and *N*-bromosuccinimide (NBS). However, this class of compounds is employed in a variety of synthetically useful transformations, including radical cyclizations,[2] the Hofmann−Löffler−Freytag reaction,[3] and elimination to give imines,[4] amongst other processes.[5]

The synthesis of *N*-halo compounds is most readily achieved by the reaction of amines or amides with electrophilic halogen sources. The most commonly employed reagents for this oxidation are sodium hypohalites (bleach and NaOBr),[6] the *N*-halo succinimides NCS and NBS,[7] and *tert*-butyl hypochlorite;[8] each has its own advantages and limitations. Sodium hypochlorite is a cheap, safe, commodity chemical, though oxidation of secondary amines (R_2NH to R_2NCl) can be plagued by modest yields and prolonged reaction times. NCS and NBS are widely utilized, but removal of the succinimide by-product is often problematic.[9] Yields with *tert*-butyl hypochlorite are generally good to excellent, but the reagent is expensive, hazardous, and suitable only for small-scale research applications.[5a,10]

We have demonstrated a practical and scalable preparation of *N*-halo compounds based on the *in situ* generation of *tert*-butyl hypohalite (*t*-BuOCl or *t*-BuOBr) under biphasic conditions.[11] Organic solutions of amines or amides are treated with aqueous sodium hypohalite (0.5−0.75 M, 1−1.5 equiv) in the presence of *tert*-butanol (0.25−1 equiv) and acetic acid (1−1.5 equiv). The *tert*-butyl hypohalite is generated slowly by the dropwise addition of the oxidant, and then reacts rapidly in the organic phase with the substrate to give the desired N−Cl or N−Br product. Slow addition of the sodium hypohalite maintains a low concentration of *tert*-butyl hypohalite present at any given time, a feature which, combined with elimination of the need for handling and manipulation of the latter reagents, makes this protocol attractive for larger-scale processing.

Table 1. Synthesis of *N*-halo compounds

Entry	Substrate	Product	Conditions[a-c]	Yield (%)[d]
1		 **3**	1/1/1/toluene/2	100
2		 **4**: X = Cl **5**: X = Br	1.5/0.5/1.5/IPAc/1	100
3			1.5/0.5/1.5/MTBE/1	98
4		 **6**	1/0.5/1/MTBE/0.5	100
5		 **7**: X = Cl **8**: X = Br	1/1/0/MTBE/0.25	100
6			1/1/0/MTBE/0.5	90
7		 **9**: X = Cl **10**: X = Br	1/0.25/1/MTBE/0.5	100
8			1.2/1/1.2/MTBE/0.5	94
9		 **11**: X = Cl **12**: X = Br	1/1/1/EtOAc/0.5	90
10			1/1/1/EtOAc/1	90
11		 **13**	1/0.5/0/MTBE/1	96
12		 **14**	1.5/1/1.5/IPAc/0.5	92
13		 **15**: Ar = *p*-F-C_6H_4	1.1/1/1.1/IPAc/1	100

[a] equiv NaOX/equiv *t*-BuOH/equiv AcOH/solvent/time (h); [b] 0.75 M aqueous NaOCl or 0.5 M aqueous NaOBr solutions were used; [c] IPAc = isopropyl acetate; MTBE = *tert*-butyl methyl ether; EtOAc = ethyl acetate; [d] Isolated yields; obtained after workup and solvent evaporation to give the desired products, which were determined to be > 95% pure by ^{1}H NMR

The conditions are mild, high yielding, and general for a variety of substrates (Table 1). Reactions are typically complete within 15−30 minutes for amines and 1−2 hours for amides. This rate differential allows for chemoselective oxidation (Entries 9 and 10). A primary amine is selectively monochlorinated (Entry 11). Amine hydrochloride salts are sufficiently acidic to promote the reaction (Entries 5, 6 and 11); no acetic acid is required for these substrates. This protocol has been demonstrated on multi-kilogram scale (Entry 13).[5a]

Following a simple workup procedure, the *N*-halo products are isolated in high purity by concentration and, if applicable, crystallization. For the *N*-halo amines, the crystalline solids (e.g. **2** and Table 1, **11** and **12**) are generally quite stable at room temperature, but the stability of the neat oils (**6**−**10**, **13**) is variable, with some (e.g. **6** and **13**) decomposing within thirty minutes. Manipulation and storage of the more sensitive non-crystalline *N*-halo amine products as solutions, in which degradation is much slower, is recommended. In contrast, all the *N*-halo amide (**3**−**5**) or sulfonamide (**14**) products were found to be very stable either in crystalline form or as neat oils.

1. Department of Process Research, Merck & Co., Inc., Rahway, NJ 07065, USA. Email: yongli_zhong@merck.com.

2. Liu, J. F.; Heathcock, C. H. *J. Org. Chem*. **1999**, *64*, 8263−8266.

3. Stocking, E. M.; Sanz-Cervera, J. F.; Unkefer, C. J.; Williams, R. M. *Tetrahedron* **2001**, *57*, 5303−5320.

4. Maughan, M. A. T.; Davies, I. G.; Claridge, T. D. W.; Courtney, S.; Hay, P.; Davis, B. G. *Angew. Chem. Int. Ed*. **2003**, *42*, 3788−3792.

5. For further selected examples, see: (a) Zhong, Y.-L., Krska, S. W.; Zhou, H.; Reamer, R. A.; Lee, J.; Sun, Y.; Askin, D. *Org. Lett*. **2009**, *11*, 369−372. (b) Drouin, A.; Lessard, J. *Tetrahedron Lett*. **2006**, *47*, 4285−4288. (c) Cossy, J.; Tresnard, L.; Pardo, D. G. *Tetrahedron Lett*. **1999**, *40*, 1125−1128. (d) Stella, L. *Angew. Chem. Int. Ed. Engl*. **1983**, *22*, 337−350. (e) Kovacic, P.; Lowery, M. K.; Field, K. W. *Chem. Rev*. **1970**, *70*, 639−655.

6. (a) Smith, J. R. L.; McKeer, L. C.; Taylor, J. M. *Org. Synth. Coll. Vol. 8* **1993**, 167−173. (c) Gassman, P. G.; Dygos, D. K.; Trent, J. E. *J. Am. Chem. Soc*. **1970**, *92*, 2084−2090.

7. (a) Zhao, M. M.; McNamara, J. M.; Ho, G.-J.; Emerson, K. M.; Song, Z. J.; Tschaen, D. M.; Brands, K. M. J.; Dolling, U. H.; Grabowski, E. J. J.; Reider, P. J. *J. Org. Chem*. **2002**, *67*, 6743−6747. (b) Snider, B. B.; Liu, T. *J. Org. Chem*. **1997**, *62*, 5630−5633. (c) Guillemin, J. C.; Denis, J. M. *Synthesis* **1985**, 1131−1133.

8. (a) Durham, T. B.; Miller, M. J. *J. Org. Chem*. **2003**, *68*, 27−34. (b) Herranz, E.; Sharpless, K. B. *Org. Synth. Coll. Vol. 7* **1990**, 223−226. (c) Gassman, P. G.; Campbell, G. A.; Frederick. R. C. *J. Am. Chem. Soc*. **1972**, *94*, 3884−3891.

9. Fieser, M. In *Reagents for Organic Synthesis*, John Wiley and Sons, New York, **1982**, Vol. 10, p 67.

10. (a) Mintz, M. J.; Walling, C. *Org. Synth. Coll. Vol. 5*, **1973**, 184−187. (b) Paquette, L. A. In *Encyclopedia of Reagents for Organic Synthesis*, John Wiley and Sons, New York, **1995**, Vol. 2, p 890.

11. Zhong, Y.-L.; Zhou, H.; Gauthier, D. R., Jr.; Lee, J.; Askin, D.; Dolling, U. H.; Volante, R. P. *Tetrahedron Lett*., **2005**, *46*, 1099−1101.

Appendix
Chemical Abstracts Nomenclature; (Registry Number)

2-Chloro-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline

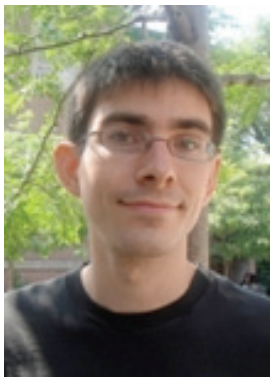
6,7-Dimethoxy-1,2,3,4-tetrahydroisoquinoline hydrochloride: Isoquinoline, 1,2,3,4-tetrahydro-6,7-dimethoxy-, hydrochloride (1:1); (2328-12-3)

Sodium hypochlorite; (7681-52-9)

tert-Butanol: 2-Methyl-2-propanol; (75-65-0)

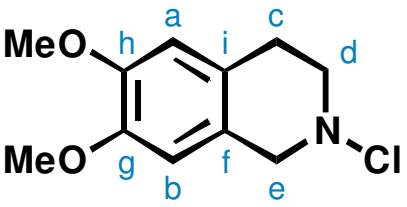
Yong-Li Zhong was born in Guangzhou, China. He received his B.S. and M.S. degrees in Chemistry from Zhongshan University under the direction of Professors Jingyu Su and Longmei Zeng. He obtained his Ph.D. in organic synthesis from the Chinese University of Hong Kong in 1998 under the supervision of Professor Tony K. M. Shing. After three years of postdoctoral studies with Professor K. C. Nicolaou at The Scripps Research Institute, he joined the Process Research Department of Merck & Co., Inc. in 2001. His research interests include the development of practical and efficient synthesis of heterocycles, and new synthetic methodologies.

Paul G. Bulger was born in London, England, in 1978. He received his undergraduate M.Chem degree in 2000 from the University of Oxford, completing his Part II project under the supervision of Dr. Mark G. Moloney. He remained at Oxford for his graduate studies, obtaining his D. Phil. in chemistry in 2003 for research conducted under the supervision of Professor Sir Jack E. Baldwin. After an enjoyable three-year stint as a postdoctoral researcher in Professor K. C. Nicolaou's group at The Scripps Research Institute, he joined the Process Research Department of Merck & Co., Inc. in the fall of 2006.



Stephen Newman was born in 1985 in Grand Falls-Windsor, Newfoundland, Canada. He studied chemistry at Dalhousie University, where he obtained his B. Sc. in 2008. During this time, he worked in the laboratory of Professor D. Jean Burnell on iron and copper catalyzed oxidative cleavage of cyclic ketones. He is currently pursuing his Ph.D. in the laboratory of Professor Mark Lautens at the University of Toronto where his research is focused on the development of methodologies for the synthesis of novel heterocycles.

400 MHz Varian NMR, $CDCl_3$



148.10
147.57
125.09
124.10
111.11
109.08
77.00
63.38
59.21
55.92
55.88
28.05

g h f i a b e d OMe c

referenced to $CDCl_3$ = 77.0, t

ppm (t1) 200 150 100 50 0

140 130 120 110
ppm (t1)

65.0 60.0 55.0 50.0 45.0 40.0 35.0 30.0
ppm (t1)

400 MHz Varian NMR, $CDCl_3$