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Synthesis of 1-*tert*-Butyl-4-chloropiperidine: Generation of an *N*-*tert*-Butyl Group by the Reaction of a Dimethyliminium Salt with Methylmagnesium Chloride

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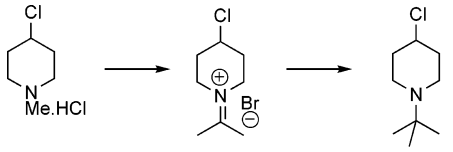
Received November 3, 2004



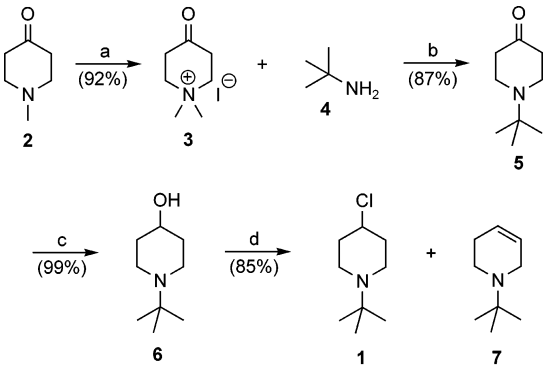
71% overall

Two efficient routes to 1-*tert*-butyl-4-chloropiperidine are described. In the first route, the key thionyl chloride mediated chlorination reaction features the use of tetrabutylammonium chloride as an additive that effectively suppresses the formation of an elimination-derived side product. In the second route, a novel alternative synthesis of 1-*tert*-butyl-4-chloropiperidine was developed in which the tertiary butyl group on the nitrogen is efficiently generated through the addition of methylmagnesium chloride to a dimethyliminium salt in 71% overall yield.

Recently, we required an efficient synthesis of 1-*tert*-butyl-4-chloropiperidine (**1**), a useful intermediate from which the 1-*tert*-butyl-4-piperidinyl Grignard reagent can be prepared in high yield. Known in the literature since 1965,[1] it transpires that the documented methods for preparing intermediate **1** are less than satisfactory from the viewpoint of a multi-kilogram scale synthesis. Consequently, we began research toward the goal of developing a reliable and productive route to 1-*tert*-butyl-4-chloropiperidine (**1**), the results of which are described herein.

Initial efforts, directed at modification of existing methodology to render it amenable to large-scale production, led to the eventual development of a four-step (four isolations) synthesis of 1-*tert*-butyl-4-chloropiperidine (**1**) (Scheme 1) starting from piperidone **2**. Of note from this work is the discovery that acrylic acid can function as an efficient and selective trap for dimethylamine (vs *tert*-butylamine **4**), allowing for facile control of the equilibrium in the conversion of quaternary salt **3** to 1-*tert*-butylpiperidone **5**. The details of this particular transformation have been previously documented.[2] Despite the significant improvement made to this transamination reaction, the overall utility of this piperidone-based route was diminished by certain problems encountered in the final chlorination step (**6** → **1**).

SCHEME 1[a]



67% overall yield of 1

[a] Reagents and conditions: (a) MeI, acetone, rt; (b) *t*-BuNH2, acrylic acid, aq NaOH, 60 °C; (c) Ra-Ni/H_2 (40 psi), EtOH; (d) $SOCl_2$, Bu_4NCl, toluene, 85 °C.

As shown in Scheme 1, 1-*tert*-butylpiperidone **5**, obtained from the Michael elimination/readdition sequence, was reduced almost quantitatively using Raney nickel.[1] The conversion of 1-*tert*-butyl-4-hydroxypiperidine **6** into 4-chloro-piperidine **1** was initially investigated using a variety of reagents. It became apparent that the thionyl chloride method[1] already described in the literature was the most applicable to the present case both in terms of cost and minimizing waste. The major issue associated with this reaction relates to a fundamental principle of organic chemistry; attempts to carry out substitution at a secondary aliphatic center will inevitably result in a varying amount of elimination side-product.[3] Indeed, the literature conditions for this reaction produced olefin **7** at around 20 mol % of the product mixture. Separation of olefin **7** from the desired product **1** is not straightforward and this level of impurity was deemed to be unacceptably large. Assuming that olefin **7** derives from an E1 elimination process, it was postulated that an increase in chloride ion concentration in the reaction mixture would suppress olefin formation by increasing the probability of simple recombination of the intermediate cation with chloride to yield chloropiperidine **1**. To test this hypothesis, we examined the use of various additives in the chlorination reaction, the results of which are summarized in Table 1.

The general trends evident in Table 1 are in accord with those predicted. Increased solvent polarity should

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‡ Department of Analytical Research.

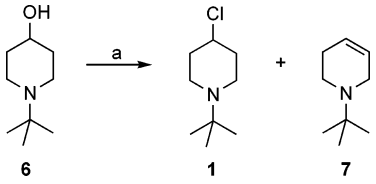
(1) (a) Robinson, J. B.; Thomas, J. *J. Chem. Soc.* **1965**, 2270. See also: (b) Fankhauser, R.; Grob, C. A.; Krasnobajew, V. *Helv. Chim. Acta* **1966**, *49*, 690.

(2) Amato, J. S.; Chung, J. Y. L.; Cvetovich, R. J.; Reamer, R. A.; Zhao, D.; Zhou, G.; Gong, X. *Org. Process Res. Dev.* **2004**, *8*, 939.

(3) For a detailed discussion of the various factors influencing substitution vs elimination see: Smith, M. B.; March, J. *March's Advanced Organic Chemistry,* 5th ed., Wiley-Interscience: New York, 2001; pages 1319−1322 and references therein.

10.1021/jo048047g CCC: $30.25
Published on Web 02/01/2005

TABLE 1[a]



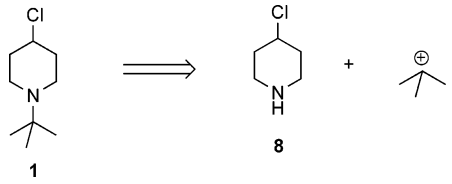
entry	solvent	Cl^- source	mol % Cl^-	% olefin **7**
1	heptane	none	0	14
2	cyclohexane	none	0	12
3	toluene	none	0	18
4	1,2-DME	none	0	35
5	toluene	none	0	58
6	toluene	LiCl	100	17
7	toluene	Me_4NCl	100	16
8	toluene	Et_4NCl	100	17
9	toluene	Bu_4NCl	100	5
10	toluene	Bu_4NCl	50	5
11	toluene	Bu_4NCl	25	9
12	toluene	Bu_4NCl	10	13
13	cyclohexane	Bu_4NCl	25	10
14	MeCN	Bu_4NCl	100	46
15	1,2-DME	LiCl	100	35

[a] Reagents and conditions: (a) SOCl, solvent, 80−85 °C, with or without chloride additive.

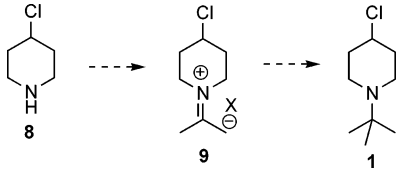
facilitate ionization of the intermediate chlorosulfinyl ester to the cation, and indeed, increased amounts of olefin were observed using solvents such as 1,2-DME or MeCN (entries 4 and 5), compared to the various hydrocarbon solvents (entries 1−3). In terms of chloride additives, simple lithium chloride and both tetramethyl- and tetraethylammonium chloride exhibit insufficient solubility in hydrocarbons (even at elevated temperatures) and consequently do not increase the concentration of chloride ion in solution (entries 6−8). Tetrabutylammonium chloride (Bu_4NCl) is soluble in toluene at 85 °C and was found to have a significant effect on the course of the reaction (entries 9−12). On a small scale, a 50 mol % charge of Bu_4NCl was found to have an optimal effect and led to a 95% isolated yield of the chloride **1**, containing 5% olefin **7**. When this optimum procedure was used on 2.7 kg of 4-hydroxy compound **6**, an improved suppression of the side-product was realized, with only 2% of olefin **7** being detected and chloropiperidine **1** isolated in 85% yield. This result demonstrates the practical control over nucleophilic substitution at a secondary center that is possible through the use of an appropriate additive that can suppress the formation of side-products resulting from elimination.

Concurrent with our development of practical experimental protocols for the piperidone-based route to 1-*tert*-butyl-4-chloropiperidine **1**, an alternative means of access to this Grignard precursor was investigated. Despite having made significant improvements with regard to several aspects of the piperidone route (Scheme 1), the use of Bu_4NCl as an additive in the chlorination reaction was considered to be a short-term solution for two reasons. First, the relatively large molecular weight of Bu_4NCl meant that for a 2.7 kg run of this reaction a charge of 2.5 kg of Bu_4NCl was required. As such, the mass charge efficiency of this reaction is low and this would almost certainly become an issue on increasing scale. Also, anhydrous Bu_4NCl proves to be relatively expensive, which is unattractive considering this reagent

SCHEME 2



SCHEME 3



is used only for side-product suppression. An obvious alternative approach to this problem is to use a commercial starting material that already contains the 4-chloro functionality. Taking this into account, a potentially simplifying retrosynthetic disconnection became apparent (Scheme 2).

To reach the desired 1-*tert*-butyl-4-chloropiperidine **1** starting from **8**, a method of alkylating the secondary nitrogen with a *tert*-butyl group was required. Inspection of the literature not only revealed sparse attempts at the direct alkylation of nitrogen using *tert*-butyl halides, but also showed these to occur in low yield.[4] The prospects for an efficient direct alkylation appeared poor, so a stepwise approach was adopted. The condensation of cyclic secondary amine perchlorates (e.g., pyrrolidine and morpholine) with acetone is known to yield the corresponding dimethyl iminium salts in good yield.[5] Also documented in the literature is the addition of nucleophilic reagents, such as Grignards, to certain iminium species.[6] Hence, it appeared reasonable that the addition of a reagent such as methylmagnesium chloride to a preformed dimethyliminium salt **9** of 4-chloropiperidine (Scheme 3) could provide a means of generating a *tert*-butyl group on this secondary nitrogen atom. To our knowledge, there are no previous literature examples in which an *N*-*tert*-butyl group is accessed in this way.[7]

4-Chloropiperidine hydrochloride **11** is commercially available but is not readily obtainable in bulk quantities and, significantly, is rather expensive. Another commercially available and closely related potential starting material is 4-chloro-1-methylpiperidine hydrochloride **10**. The *N*-methyl compound **10** is approximately eight times less expensive than 4-chloropiperidine hydrochloride **11**. Consequently we elected to pursue a demethylation strategy (Scheme 4), and indeed, the use of 1-chloroethyl chloroformate (ACE-Cl)[8] led to clean demethylation to

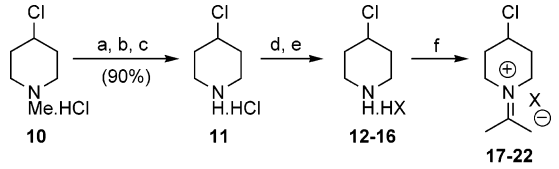
(4) For direct tertiary alkylation of oxygen to form *tert*-butyl ethers, see: Masada, H.; Gotoh, H.; Ohkubo, M. *Chem. Lett.* **1991**, *10*, 1739. Failed pyridone *N*-alkylation: Sato, T.; Yoshimatsu, K.; Otera, J. *Synlett* **1995**, *8*, 845. Pyrazole alkylation: Elguero, J.; Jaquier, R.; Tien Duc, H. C. N. *Bull. Soc. Chim. Fr.* **1966**, 3727.

(5) Leonard, N. J.; Paukstelis, J. V. *J. Org. Chem.* **1963**, *28*, 3021.

(6) For examples, see: (a) Courtois, G.; Miginiac, P. *Bull. Soc. Chim. Fr.* **1982**, 395. (b) Miyano, S.; Yamashita, O.; Sumoto, K.; Shima, K.; Hayashimatsu, M.; Satoh, F. *J. Heterocycl. Chem.* **1987**, *24*, 271.

(7) For a conceptually similar report on the addition of methylmagnesium bromide to nitrones as a means of generating *tert*-butyl groups on nitrogen, see: Schwartz, M. A.; Hu, X. *Tetrahedron Lett.*, **1992**, *33*, 1689.

SCHEME 4[a]



Entry	Amine salt	Iminium salt
1	**11**	**17** (X = Cl, 0%)
2	**12** (X = OTf, 92%)	**18** (X = OTf, 99%)
3	**13** (X = Br, 90%)	**19** (X = Br, 87%)
4	**14** (X = O_3SMe, 91%)	**20** (X = O_3SMe, 0%)
5	**15** (X = O_2CCF_3, 89%)	**21** (X = O_2CCF_3, 0%)
6	**16** (X = OTs, 90%)	**22** (X = OTs, 0%)

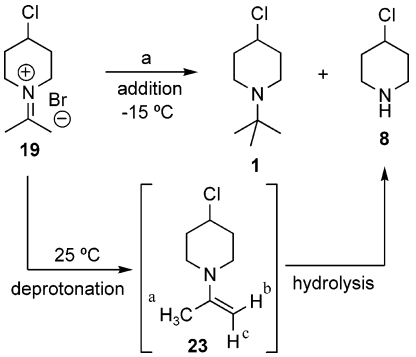
[a] Reagents and conditions: (a) aq K_2CO_3/1,2-DCE; (b) ACE-Cl, 0 to 80 °C; (c) MeOH, 65 °C; (d) aq K_2CO_3/MTBE; (e) HX; (f) 2,2-dimethoxypropane, MeCN, 70 °C.

afford a 90% yield of 4-chloropiperidine hydrochloride **11** in a one-pot reaction.

The hydrochloride salt **11**, obtained directly from the demethylation reaction for iminium formation, has low solubility in various solvent mixtures, which precluded any appreciable rate of reaction. As a result, a variety of alternative acid salts (**12**−**16**) of 4-chloropiperidine were prepared and then tested in the iminium formation. From this screen, the triflate and hydrobromide salts (**12** and **13**) emerged as good candidates for efficient iminium production and these were then studied in some detail. The triflic acid salt **12** furnished a homogeneous reaction mixture using 2,2-dimethoxypropane (DMP) as solvent and essentially quantitative conversion to the iminium **18** was observed within 3 h by NMR analysis. Under similar conditions, using MeCN as cosolvent, hydrobromide salt **13** is only partially soluble but nevertheless steadily converts to the iminium species **19**. Significantly, and in contrast to the triflate case, iminium bromide **19** has low solubility in the DMP/MeCN mixture, causing **19** to precipitate cleanly as a white solid. Importantly, no Finkelstein-type exchange of the 4-chloro substituent was observed under the reaction conditions. Optimal results were achieved at an overall concentration of 0.25 M and using a 1:1 mixture of DMP−MeCN, leading to a reproducible yield of 87−89% of iminium salt **19**, isolated by simple filtration of the reaction mixture.

The addition of a methyl nucleophile to the iminium salt **19** was initially attempted using a Grignard reagent (Scheme 5). A THF slurry of pure iminium salt was treated with methylmagnesium chloride at 25 °C, which resulted in a colorless and homogeneous solution upon warming to room temperature. After aqueous workup, the desired 1-*tert*-butyl-4-chloropiperidine **1** was isolated alongside one other product that was identified by NMR as 4-chloropiperidine **8**. Direct NMR analysis of the reaction mixture before aqueous quench revealed the presence of enamine **23** (hydrolyzed upon aqueous workup to **8**), as indicated by the distinctive signals at 3.86 ppm (H_c, q, J = 0.8 Hz, 1H), 3.85 ppm (H_b, s, 1H) and

SCHEME 5[a]



[a] Reagents and conditions: (a) MeMgCl, THF, −15 or 25 °C.

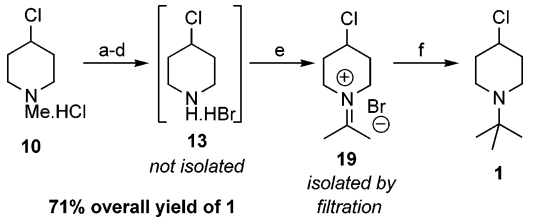
1.90 ppm (H_a, d, J = 0.8 Hz, 3H). Clearly, deprotonation of one of the methyl groups of the iminium salt was competing with the desired addition reaction, and indeed, this served to explain the small amount of effervescence observed during addition of the Grignard (loss of methane). With this information in hand, a series of experiments were conducted to uncover the optimal conditions for this reaction. Sources of methyl anion tested included methyllithium and methyllithium−lithium bromide complex, methyl Grignards with chloride, bromide and iodide counterions, and dimethylzinc. Several solvents and temperatures for the reaction were also investigated since it is well-known that these parameters can significantly influence the aggregation state of organometallic species and therefore the relative nucleophilicity vs basicity of these reagents.[9] From this study it was determined that the best results toward the preparation of **1** could be achieved using methylmagnesium chloride in THF at reduced temperature (−15 °C). Under these conditions, smooth conversion to the desired 1-*tert*-butyl-4-chloropiperidine **1** is observed with less than 5% of iminium deprotonation and piperidine **8** can be easily removed during mildly acidic aqueous workup by taking advantage of its increased basicity relative to the desired product **1** (unhindered secondary amine vs hindered tertiary amine). Concentration of the final MTBE solution affords 95% yield of 1-*tert*-butyl-4-chloropiperidine **1** (with 99% GC purity) containing none of the olefinic side product **7** observed during the chlorination step in the piperidone chemistry.

As noted above, it was necessary to convert the HCl salt **11** into the corresponding HBr salt **13** for the subsequent iminium formation. Although fairly simple on paper, this change of acid salt is less than optimal in the general sense that it adds an isolation step to the overall synthesis of 1-*tert*-butyl-4-chloropiperidine via this route. Further, and specific to this case, are the problems associated with the volatility of 4-chloropiperidine (**8**) if the HBr salt formation requires prior azeotropic drying and/or solvent switching. There are also operational difficulties linked with the use of a corrosive gas such as hydrogen bromide. Consequently, an alternative method was sought. Based on the difference in solubility between sodium bromide and sodium chloride,

(8) Olofson, R. A.; Martz, J. T.; Senet, J.-P.; Piteau, M.; Malfroot, T. *J. Org. Chem.*, **1984**, *49*, 2081.

(9) For example: Briggs, T. F.; Winemiller, M. D.; Collum, D. B.; Parsons, R. L., Jr.; Davulcu, A. H.; Harris, G. D.; Fortunak, J. M.; Confalone, P. N. *J. Am. Chem. Soc.* **2004**, *126*, 5427.

SCHEME 6[a]



[a] Reagents and conditions: (a) aq K_2CO_3/1,2-DCE; (b) ACE-Cl, 0 to 80 °C; (c) MeOH, 65 °C; (d) NaBr, MeOH; (e) 2,2-dimethoxypropane, MeCN, 70 °C; (f) MeMgCl, THF, −15 °C.

it seemed reasonable that a simple counterion exchange could be achieved by treating the HCl salt with sodium bromide in a suitable solvent. Thus, following treatment of a methanol solution of the HCl salt with 5 equiv of NaBr at room temperature, a heterogeneous mixture was obtained. Filtration removed the precipitated NaCl and concentration of the filtrate left the HBr salt alongside some excess NaBr that had remained in solution. Capillary electrophoresis on the isolated solid verified that counterion exchange had occurred. Further, a use-test of the material in the iminium formation gave essentially the same result as that obtained using the standard HBr salt. Based on these findings it was possible to telescope the anion exchange step back into the previous demethylation reaction since this step directly affords a MeOH solution of the HCl salt. Thus, the entire demethylation/counterion exchange sequence proceeded smoothly and afforded material that performed satisfactorily in the iminium formation. Last, in a further refinement to this process, it was discovered that the NaCl produced during the counterion exchange need not be filtered off before iminium formation. As such, the chemistry can be conducted as a through process beginning with the *N*-methyl salt **10** and featuring no isolations until iminium bromide **19**. Only 1.2 equiv of NaBr are required and the resultant mixture of piperidine salt **13**, NaBr and NaCl can simply be solvent switched into the appropriate quantity of MeCN for the next step. As a result, the synthesis of 1-*tert*-butyl-4-chloropiperidine **1** via the iminium route can be achieved in 71% overall yield starting from 4-chloro-1-methylpiperidine hydrochloride **10** and involves only two isolations (Scheme 6).

In summary, several important modifications to published procedures were developed that allowed for the rapid synthesis of multi-kilogram quantities of 1-*tert*-butyl-4-chloropiperidine (**1**) starting from 1-methyl-4-piperidone (**2**).[2] In particular, a degree of control over the conversion of a secondary alcohol to the corresponding chloride was achieved through the use of Bu_4NCl as an additive. During this campaign, several long-term drawbacks with the piperidone route were identified and this fueled investigations toward an alternative synthesis. Ultimately, we developed an efficient novel approach, which furnishes the targeted intermediate in 71% overall yield and 99% purity and involves only two isolations. To the best of our knowledge, the iminium salt formation/methyl Grignard addition sequence has not previously been documented as a method for the introduction of a *tert*-butyl group onto a secondary nitrogen.

Supporting Information Available: Full experimental procedures and analytical data. This material is available free of charge via the Internet at http://pubs.acs.org.

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