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Reductive Chlorination and Bromination of Ketones via Trityl Hydrazones

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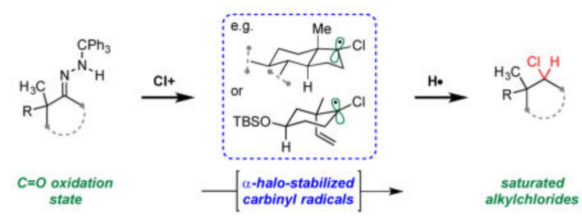
Abstract

A method is presented for the direct transformation of a ketone to the corresponding reduced alkyl chloride or bromide. The process involves the reaction of a ketone trityl hydrazone with t-BuOCl to give a diazene that readily collapses to the α-chlorocarbinyl radical, reduction of which by a hydrogen atom source gives the alkyl chloride product. The use of N-bromosuccinimide provides the corresponding alkyl bromide. This unique transformation provides a reductive halogenation that complements Barton's redox-neutral vinyl halide synthesis.

Graphical Abstract



Halogen first, then hydrogen: Trityl hydrazones may be transformed by action of halonium ion sources to α-chloro and α-bromo carbinyl radicals, reduction of which affords the corresponding alkyl chlorides and alkyl bromides. Notably, this unique transformation is able to efficiently construct homoallylic and neopentyl chlorides and provides a reductive hydrazone halogenation complementary to Barton's

Keywords

Hydrazones; Radical Reactions; Chlorination; Bromination; Diastereoselectivity

The transformation of an alcohol to a chloride, one of the most basic reactions in organic chemistry, can present unanticipated difficulties when encountered in a complex molecule. In the course of studies toward the synthesis of *N*-methylwelwitindolinone B isothiocyanate (**1**, Figure 1), we attempted to convert the C-13 hydroxyl of **2** to the required, inverted

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chloride.[1] Unfortunately, the neopentyl and homoallylic nature of the alcohol conspired to trigger a skeletal rearrangement, thereby foiling the planned synthetic route.[2] Others have also observed difficulties, in completely different systems, in making alkyl chlorides by Walden inversion of suitably activated precursors.[3] Given the limitations of this transformation, combined with the prevalence of natural products[4] having a chloride attached to an sp^3-hybridized carbon, we set forth to devise a fundamentally different solution for the synthesis of such chlorides.[5] We report here the realization of a method for the overall reductive transformation of ketones to alkyl halides.

The reductive chlorination method was conceived to provide a conceptually new way for the installation of a chlorine atom in high-value compounds. Rather than introducing the chloride through nucleophilic displacement of an activated alcohol, with the attendant difficulties and complications noted above, the idea was to introduce the chlorine first and then, through the generation of a reactive intermediate, add a hydrogen atom. This concept was expected to be realized through the use of hydrazone chemistry (Figure 2a).[6–8] The reaction of a trityl hydrazone with a chloronium source was expected to give a chlorodiazene (**5**),[9] which on thermolysis would extrude N_2 to generate a trityl radical and the sought after reactive intermediate, α-chlorocarbinyl radical **6**. Provided the thermolysis were carried out in the presence of a hydrogen atom donor, then diastereoselective hydrogen abstraction would give the desired chloroalkane product. Introduction of chlorine and generation and reduction of the reactive intermediate were envisioned though a single synthetic maneuver. Realized, this transformation provides a reductive chlorination from the C=O oxidation state, a method that complements Barton-type vinyl halide synthesis (Figure 2b).[10–11]

Feasibility of the above concept was evaluated using hydrazone **11a**, available through condensation of trityl hydrazide and benzylacetone (74%).[12] Treatment of a solution of **11a** in THF with *t*-BuOCl (1.1 equiv) at −20 °C followed by addition of an excess of EtSH and warming to room temperature afforded the desired product of reductive chlorination in 37% yield (NMR).[13] Modest yields in these early reactions were balanced significantly by the product of apparent hydrolysis of the starting hydrazone, benzylacetone. Mechanistic considerations suggested that the apparent “hydrolysis product” likely arises by way of peroxychloroalkane intermediate **14**, the product of O_2 capture by the α-chlorocarbinyl radical (Figure 3). Support for this hypothesis was obtained by carrying out the thermolysis in the absence of a reducing agent and placing it under an oxygen balloon prior to warming to room temperature. The major product of the reaction under these conditions was benzylacetone (57%, NMR), with no evidence of chloroalkane **13a**. On the other hand, scrupulous exclusion of air through two freeze-pump-thaw cycles completely eliminated formation of ketone **10** in the reaction product. Variable temperature NMR experiments provided an understanding of the thermal requirements for the different steps of the reaction.[14–15] A −78 °C sample of hydrazone **11a** and *t*-BuOCl was examined by NMR in a probe pre-cooled −30 °C. After 10 minutes had elapsed, a reaction was observed, and the starting hydrazone was found to be fully consumed. The resulting putative chlorodiazene **12** was found to persist as the temperature was increased from −30 °C to −10 °C. Upon further warming above −10 °C, diazene **12** decomposed to give a mixture of products. With the sequence of reagent addition and temperature control guided by the above study, as well as careful O_2 exclusion, the reaction was optimized to furnish **13a** in 82% isolated yield (Table 1, entry 1). A brief screen of chloronium ion sources and H-atom donors offered no improvement over *t*-BuOCl and EtSH, with *N*-chlorosuccinimide yielding none of the desired chloride. Less odorous, high molecular weight thiols were examined briefly as hydrogen atom donors, but found to give less satisfactory results.

The capability of the reductive chlorination procedure was examined in a range of substrates, as shown in Table 1. The hydrazone of phenoxyacetone was converted to the corresponding chloride in 85% yield (entry 2). Diastereoselectivity in the reduction event displayed high substrate dependence. Substrates in which the hydrazone was part of a conformationally-locked six-membered ring favored axial hydrogen abstraction to give the equatorial chloride. Reductive chlorination of **11c** and **11d** gave a mixture of chlorides, favoring the equatorial chlorides by ca. 3:1 (entries 3 and 4). Diminished selectivity was observed for the reaction of the hydrazone of *trans*-1-decalone, wherein the three 1,3-diaxial interactions may disfavor axial hydrogen abstraction (entry 5). The neopentyl, homoallylic hydrazone **11g**, comprising the cyclohexane core of welwitindolinone B, gave a 2.8:1 mixture of chloride diastereomers, from which the major component (**13g**) was isolated in 50% yield. Notably, this reductive chlorination occurs without 1,2-migration of the vinyl group, possibly reflecting the radical stabilizing effect of chlorine.[16]

Among cyclopentanone-derived trityl hydrazones, the facial bias of the [2.2.1]-bridged system in **11h** engendered high selectivity for the *endo* chloride **13h**, isolated in 83% yield, with greater than 20:1 diastereoselectivity. The hydrazone of (−)-α-thujone (**11i**) gave a mixture of chlorides **13i** in 70% yield, wherein hydrogen abstraction had taken place predominantly from the face opposite the α-methyl substituent.[17] The utility of this method was further demonstrated by the reductive chlorination of sterically encumbered hydrazone **11j**, derived from *O*-Me estrone. The lower reactivity of hydrazone **11j** to chlorination necessitated deprotonation followed by chlorination, achieved efficiently with dichloramine-T. The protocol afforded chloride **13j** in good yield and high selectivity for the β-chloride shown, with hydrogen abstraction taking place *anti* to the adjacent C-13 methyl group.

The underlying concept of the reductive chlorination appeared transferrable to bromination. Thus, upon treatment of hydrazone **11a** with *N*-bromosuccinimide (NBS) in place of *t*-BuOCl, followed by addition of EtSH and warming, it was converted to the expected reductive bromination product **16a** (Table 2). Three other hydrazones were similarly subjected to the bromination conditions and gave the anticipated alkyl bromides in good yields. Of note, hydrogen abstraction by the α-bromocarbinyl radicals gave consistently lower diastereoselectivities than that observed for their α-chloro congeners, with apparent selectivity reversal in the bromination of *trans*-1-decalone (**16e**). The effect of the different halides on selectivity appears to parallel that observed for other free radical processes, including halogenations of alkanes. The slightly higher selectivity seen for reductive chlorination vs bromination comports with greater stabilization of the radical accorded by chlorine over bromine, as reflected by C-H bond dissociation energies of simple haloalkanes.[18]

In summary, we have disclosed a novel method for the conversion of ketones to the respective saturated alkyl chlorides. The key step involves chlorination of a ketone trityl hydrazone, which upon warming fragments to give an α-halo-stabilized carbinyl radical that is then reduced by EtSH to furnish the alkyl chloride product. The method is effective with a range of trityl hydrazones, and affords chloride products with stereoselectivities that may complement those available through ionic processes. The basic transformation was also successfully demonstrated for the synthesis of alkyl bromides.[19] The ability of this method to efficiently construct neopentyl alkyl chlorides from the carbonyl functional group provides a distinct tactic for the preparation of such halide-containing natural products, syntheses of which are of ongoing interest in our laboratories.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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6. For general reviews of hydrazone chemistry: a)Rogen BA, El-Awa A. “Hydrazine,” e-EROS Encyclopedia of Reagents for Organic Synthesis. 2014. 1–7. b)Chamberlin AR, Sheppeck JE, Goess B, Lee C. “p-Toluenesulfonylhydrazide,” e-EROS Encyclopedia of Reagents for Organic Synthesis. 2007. 1–11. c)Robinson B. Chem Rev. 1963; 63: 373–401. d)Robinson B. Chem Rev. 1969; 69: 227–250.
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12. Please see Supporting Information.
13. (a) Among the by-products were triphenylmethane and ethyl trityl sulphide. For a recent review regarding thiyl radicals, including the use of thiols as H-atom donors, see: (b)Dénès F, Pichowicz M, Povie G, Renaud P. Chem Rev. 2014; 114: 2587–2693. [PubMed: 24383397]
14. Please see Supporting Information for selected ^{1}H NMR spectra (Figure S1).
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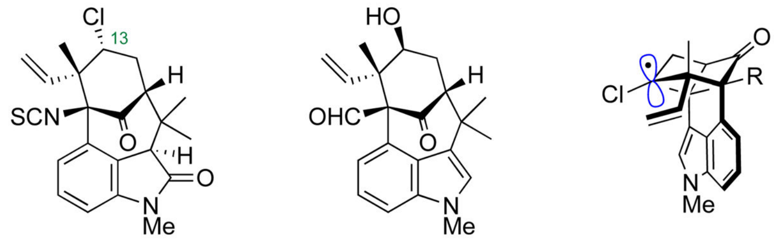
19. In preliminary studies, we have found that lithiation of benzylacetone trityl hydrazone 11a followed by treatment with NFSI generated the corresponding fluoride in 33% yield (NMR, unoptimized).



N-methylwelwitindolinone B isothiocyanate (**1**) **2** **3**

Figure 1.
Welwitindolinone B and potential precursors.

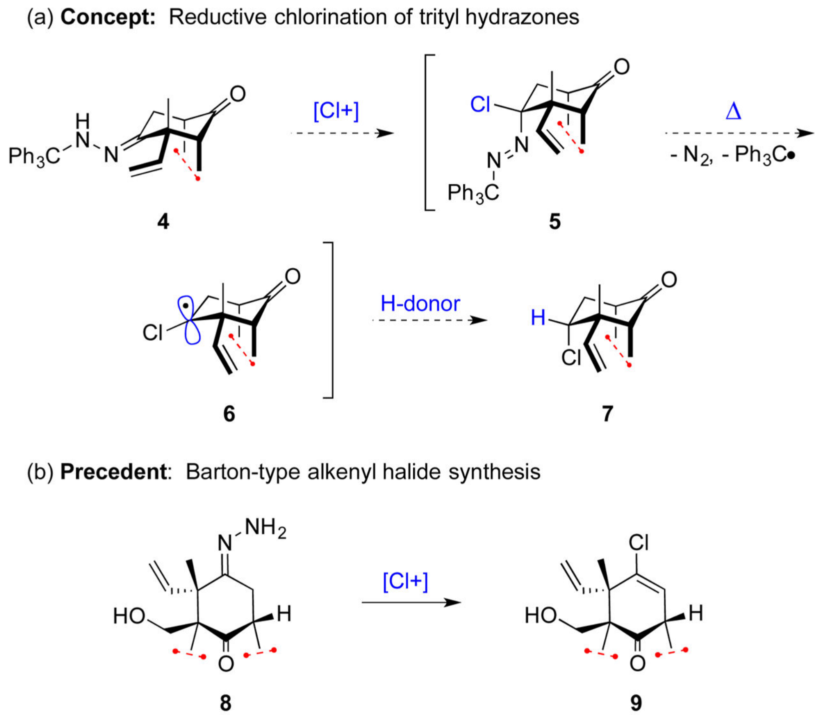


Figure 2.

Synthesis of organochlorides from hydrazone precursors.

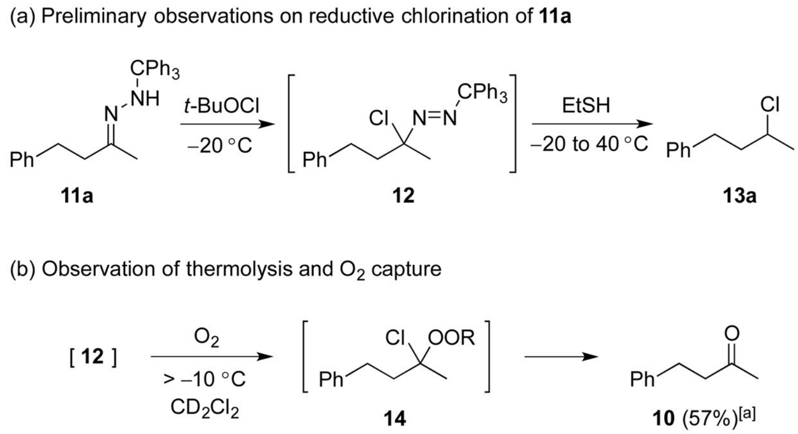
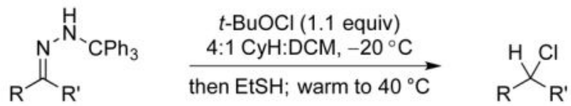


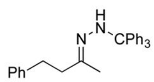
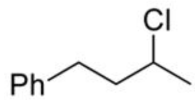
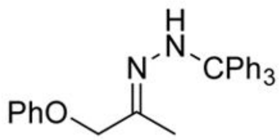
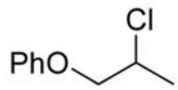
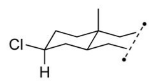
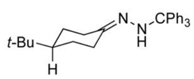
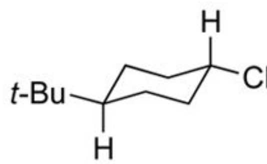
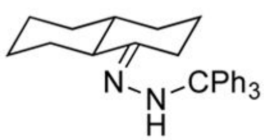
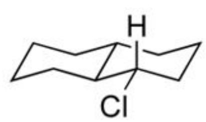
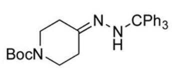
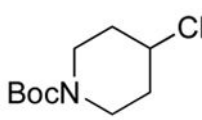
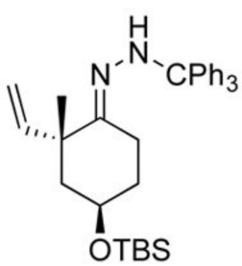
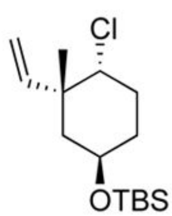
Figure 3.

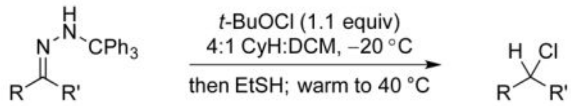
Optimization of reaction parameters. [a] Reactions performed in THF; NMR yield.

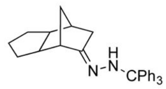
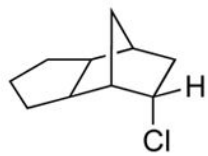
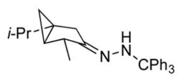
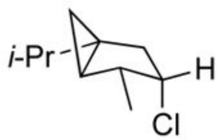
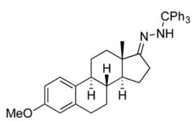
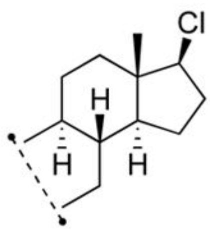
Table 1

Reductive chlorination of trityl hydrazones.



entry	hydrazone	chloride	yield[a]
1 **11a**			**13a** 82%
2 **11b**			**13b** 85%[b]
3 **11c**			**13c** 57% (3.4:1)
4 **11d**			**13d** 69% (2.9:1)
5 **11e**			**13e** 71% (1.3:1)
6 **11f**			**13f** 56%[b]
7 **11g**			**13g** 50%[c]



entry	hydrazone	chloride	yield[a]
8 **11h**			**13h** 83% (21:1)
9 **11i**			**13i** 70% (2.6:1)
10 **11j**			**13j** 67%[d]

[a]Isolated yields; diastereomeric ratio (dr) determined by ^{1}H NMR of purified chlorides and indicated in parentheses.

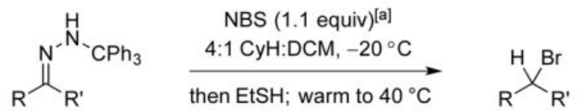
[b]NMR yield.

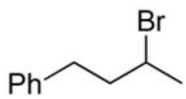
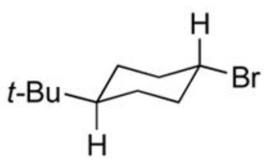
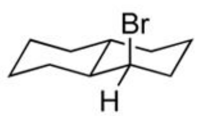
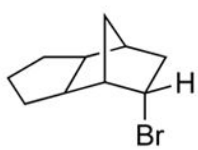
[c]Isolated yield for diastereomer shown (major), 2.8:1 crude dr.

[d]Lithiated hydrazone treated with dichloramine-T.

Table 2

Reductive bromination of trityl hydrazones.



hydrazone	bromide	yield[b]	dr[c]
11a		**16a** 65%	-
11d		**16d** 69%	2.5:1
11e		**16e** 49%	1.1:1
11h		**16h** 60%	17:1

[a] NBS solubilized in THF.

[b] Isolated yields.

[c] Diastereomeric ratio (dr) determined by ^{1}H NMR of purified bromides.