Working with Hazardous Chemicals

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.

In some articles in *Organic Syntheses*, chemical-specific hazards are highlighted in red “Caution Notes” within a procedure. It is important to recognize that the absence of a caution note does not imply that no significant hazards are associated with the chemicals involved in that procedure. Prior to performing a reaction, a thorough risk assessment should be carried out that includes a review of the potential hazards associated with each chemical and experimental operation on the scale that is planned for the procedure. Guidelines for carrying out a risk assessment and for analyzing the hazards associated with chemicals can be found in Chapter 4 of Prudent Practices.

The procedures described in *Organic Syntheses* are provided as published and are conducted at one’s own risk. *Organic Syntheses, Inc.*, its Editors, and its Board of Directors do not warrant or guarantee the safety of individuals using these procedures and hereby disclaim any liability for any injuries or damages claimed to have resulted from or related in any way to the procedures herein.

*These paragraphs were added in September 2014. The statements above do not supersede any specific hazard caution notes and safety instructions included in the procedure.*
ALLYLICALLY TRANSPOSED AMINES FROM ALLYLIC ALCOHOLS: 3,7-DIMETHYL-1,6-OCTADIEN-3-AMINE

[1,6-Octadien-3-amine, 3,7-dimethyl-]

1. Procedure

Caution! Part A should be carried out in a well-ventilated hood to avoid exposure to trichloroacetonitrile vapors.

A. Geraniol trichloroacetimidate (1). A dry, 250-ml., three-necked flask is equipped with a magnetic stirring bar, a pressure-equalizing dropping funnel, a thermometer, and a nitrogen inlet tube. The apparatus is flushed with nitrogen and charged with 410 mg. (0.0103 mole) of sodium hydride dispersed in mineral oil (Note 1) and 15 ml. of hexane. The suspension is stirred, and the hydride is allowed to settle. The hexane is removed with a long dropping pipette, 60 ml. of anhydrous diethyl ether is added, and a solution of 15.4 g. (0.0993 mole) of geraniol in 15 ml. of anhydrous ether is added over 5 minutes. After the evolution of hydrogen ceases (less than 5 minutes), the reaction mixture is stirred for an additional 15 minutes. The clear solution is then cooled to between −10 and 0° in an ice–salt bath. Trichloroacetonitrile (10.0 ml., 14.4 g., 0.0996 mole) is added dropwise to the stirred solution, while the reaction temperature is maintained below 0° (Note 2). Addition is completed within 15 minutes, and the reaction mixture is allowed to warm to room temperature. The light amber mixture is poured into a 250-ml., round-bottomed flask, and the ether is removed with a rotary evaporator. Pentane [150 ml., containing 0.4 ml. (0.01 mole) of methanol] is added, the mixture is shaken vigorously for 1 minute, and a small amount of dark, insoluble material is removed by gravity filtration. The residue is washed two times with pentane (50 ml. total), and the combined filtrate is concentrated with a rotary evaporator, yielding 27–29 g. (90–97%) of nearly pure (Note 3) imidate 1.

B. 3,7-Dimethyl-3-trichloroacetamido-1,6-octadiene (2). A 500-ml., round-bottomed flask equipped with a condenser, a magnetic stirring bar, and a calcium chloride drying tube is charged with imidate 1...
and 300 ml. of xylene. The solution is refluxed for 8 hours (Note 4). After cooling to room temperature the dark xylene solution is filtered through a short column (4.5 cm. in diameter) packed with silica gel (70 g.) and toluene. The column is eluted with an additional 250 ml. of toluene, and the combined light yellow eluant is concentrated with a rotary evaporator. Vacuum distillation through a 15-cm. Vigreux column yields 20–22 g. (67–74% for the two steps) of octadiene 2 as a colorless liquid, b.p. 94–97° (0.03 mm.) (Note 5).

C. 3,7-Dimethyl-1,6-octadien-3-amine (3). A 500-ml. round-bottomed flask equipped with a magnetic stirring bar, a condenser, and a nitrogen inlet tube is charged with 9.0 g. (0.030 mole) of octadiene 2, 160 ml. of 95% ethanol, and 150 ml. of aqueous 6 N sodium hydroxide. The air is replaced with nitrogen (Note 6), and the solution is stirred at room temperature for 40 hours (Note 7). Ether (300 ml.) is added, the organic layer is separated, and the aqueous layer is washed twice with 50 ml. of ether. After drying over anhydrous potassium carbonate and filtration, the organic extracts are concentrated with a rotary evaporator, affording a white, semisolid residue, which is extracted four times with 50 ml. of boiling hexane. The extract is concentrated with a rotary evaporator, and the residual yellow liquid is distilled under reduced pressure using a short-path apparatus, yielding 2.99–3.45 g. (65–75%) of amine 3, b.p. 58–61° (2.6 mm.) (Note 8) and (Note 9).

2. Notes

1. The reagents used in this procedure were obtained from the following sources: geraniol (99+%), Aldrich Chemical Company, Inc.; sodium hydride (58% dispersion in mineral oil), Alfa Products, Division of the Ventron Corporation; trichloroacetonitrile, Aldrich Chemical Company, Inc.; xylene (a mixture of isomers, b.p. 137–144°), Mallinckrodt Chemical Works; anhydrous ether, Mallinckrodt Chemical Works; Silica Gel (Grade 62), Grace Davison Chemical. The reagents used by the checkers were obtained from the following sources: geraniol (98.7%), sodium hydride (58% dispersion in mineral oil), trichloroacetonitrile, and xylene (a mixture of isomers, b.p. 137–143°), Fluka A G, Chemische Fabrik, Buchs, Switzerland; Silica gel (70–230 mesh ASTM), E. Merck A G, Darmstadt, Germany.

2. For secondary or tertiary alcohols, the yields are improved by adding the alcohol–alkoxide solution dropwise to a solution of trichloroacetonitrile and ether at 0°.

3. The crude imidate 1 is sufficiently pure (checked by 1H NMR) for most purposes and can be used in the next step without further purification. IR (neat) cm⁻¹: 3340 weak (N-H), 1660 strong (C=O); 1H NMR (CCl₄), δ (multiplicity, coupling constant J in Hz., number of protons, assignment): 1.58 (s, 3H, CH₃), 1.66 (s, 3H, CH₃), 1.73 (s, 3H, CH₃), 4.77 (d, J = 7, 2H, H₁), 5.1 (broad s, 1H, H₂), 5.5 (approx. t, J = 7, 1H, H₃), 8.3 (broad s, 1H, NH). The crude imidate 1 may be distilled rapidly through a short Vigreux column to give 24–28 g. (80–93%) of distilled product, b.p. 109–111° (0.1 mm.). However, the checkers found by 1H NMR analysis that this product already contains substantial amounts of octadiene 2 formed by thermal rearrangement during distillation.

4. The reaction can be conveniently monitored in the IR by observing the decrease in the C=N stretching absorption at 1660 cm⁻¹ or by TLC [silica, developed with hexane–ethyl acetate (9 : 1) or (4 : 1)].

5. The octadiene 2 appears pure by 1H NMR and elemental analysis. A TLC [silica, developed with hexane–ethyl acetate (4 : 1), visualized with 5% ceric ammonium nitrate in 20% sulfuric acid and heating] shows a major spot at Rf = 0.4 and a very small impurity at 0.7. The trace impurity may be removed by crystallization from hexane at −78°. The checkers found that a GC (2% Silicone OV-17 on Gaschrom Q., 80–100 mesh, 200 × 0.22 cm., 120°) showed one major peak (97.0–97.2%) at a relative retention value of 1.00 (17.3 minutes, nitrogen, 30 ml. per minute), and a minor peak at 0.94 (<3%). The octadiene 2 has the following spectral properties: IR (neat) cm⁻¹: 3423 and 3355 weak (N-H), 1722 strong (C=O), 1504 strong (CO-NH₂, amide II band), 983 weak and 915 medium (CH=CH₂); 1H NMR (CDCl₃), δ (multiplicity, coupling constant J in Hz., number of protons, assignment): 1.49 (s, 3H, CH₃), 1.60 (s, 3H, CH₃), 1.67 (s, 3H, CH₃), 4.9–5.3 (m, 3H, H₁ and H₂), 5.96 (approx. d of d, J = 9.5 and 18.5, 1H, H₃), 6.6 (broad s, 1H, NH; 13C NMR (acetone-d₆), δ (assignment): 159.8 (C=O), 141.1 (C₂), 132.4 (C₁), 123.4 (C₆), 113.2 (C₃), 93.3 (C₁₁), 58.7 (C₇), 38.8 (C₄), 25.7 (CH₃), 23.9 (CH₃), 22.5 (C₅), 17.5 (CH₃).

6. The apparatus described in Org. Synth., Coll. Vol. 4, 132 (1963) was used to maintain a nitrogen atmosphere.

7. The reaction time may be cut to less than 1 hour by running the reaction at reflux, but the yield is 5–
10% lower. The checkers found that under these conditions the weight yield of the distilled product was 67–70%. However, GC (3% Silicone GE-SE-30 on Gaschrom Q, 80–100 mesh, 200 × 0.22 cm., 60°) showed that the product contained substantial amounts (19–23%) of an unidentified by-product having a relative retention value of 1.22 (nitrogen, 30 ml. per minute) and a minor peak at 0.96 (<2%). The checkers also found that the reaction can be conveniently monitored by TLC [silica, hexane–ethyl acetate (4 : 1)].

8. The checkers found that the crude amine \(3\) (linalylamine) is more conveniently distilled at a pressure of 11–12 mm.

9. A GC (10% Carbowax 20 M–2% KOH on Chromosorb W, AW, 80–100 mesh, 180 × 0.3 cm., 90°) showed one major peak (99%) at a relative retention value of 1.00 (3.5 minutes, nitrogen, 50 ml. per minute), and a minor peak at 1.1 (<1%). Temperature programming to 200° detected the presence of several higher-boiling trace impurities (<1%). The checkers found that a GC (3% Silicone GE-SE-30 on Gaschrom Q, 80–100 mesh, 200 × 0.22 cm., 60°) showed one major peak (97.9–98.4%) at a relative retention value of 1.00 (11.8 minutes, nitrogen, 30 ml. per minute), and a minor peak at 0.96 (<2.1%). IR (neat) cm\(^{-1}\): 3345 and 3301 weak (N-H), 996 and 912 medium (CH=CH\(_2\)); \(^1\)H NMR (CCl\(_4\)), \(\delta\) (multiplicity, coupling constant \(J\) in Hz., number of protons, assignment): 1.08 (s, 3H, CH\(_3\)), 1.55 (s, 3H, CH\(_3\)), 1.63 (s, 3H, CH\(_3\)), 4.7–5.2 (m, 3H, H\(_1\) and H\(_6\)), 5.84 (approx. d of d, \(J = 10.1\) and 17.8, 1H, H\(_2\)).

3. Discussion

This procedure illustrates a general method for the preparation of rearranged allylic amines from allylic alcohols.\(^2,3\) The method is experimentally simple and has been used to prepare a variety of allylic \(n\)-, \(sec\)-, and \(tert\)-carbonyl amines, as illustrated in Table I. The only limitation encountered so far is a competing ionic elimination reaction which becomes important for trichloroacetimidic esters of 3-substituted-2-cyclohexenols,\(^3,4\) The rearrangement is formulated as a concerted \([3,3]\)-sigmatropic rearrangement on the basis of its stereo- and regiospecificity\(^3,5\) which are similar to those observed in related \([3,3]\)-sigmatropic processes.\(^6\) In certain cases the allylic imidate rearrangement may be accomplished at or below room temperature by the addition of catalytic amounts of mercury(II) salts.\(^2,3\)

<table>
<thead>
<tr>
<th>Alcohol</th>
<th>Trichloroacetamide Product</th>
<th>Overall Isolated Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>((E))-2-Hex-1-ol</td>
<td>3-Trichloroacetamido-1-hexene</td>
<td>72</td>
</tr>
<tr>
<td>Cinnamyl alcohol</td>
<td>3-Phenyl-3-trichloroacetamido-1-propene</td>
<td>76</td>
</tr>
<tr>
<td>1-Hepten-3-ol</td>
<td>((E))-1-Trichloroacetamido-2-heptene</td>
<td>74</td>
</tr>
<tr>
<td>2-Cyclohexen-1-ol</td>
<td>3-Trichloroacetamido-1-cyclohexene</td>
<td>61</td>
</tr>
<tr>
<td>Linalool</td>
<td>3,7-Dimethyl-1-trichloroacetamido-2,6-octadiene(^a)</td>
<td>83</td>
</tr>
<tr>
<td>3,5,5-Trimethyl-2-cyclohexen-1-ol</td>
<td>3,5,5-Trimethyl-3-trichloroacetamido-1-cyclohexene</td>
<td>10–43</td>
</tr>
<tr>
<td>3-(4,4-Ethylenedioxybutyl)-2-cyclohexen-1-ol</td>
<td>3-(4,4-Ethylenedioxybutyl)-3-trichloroacetamido-1-cyclohexene</td>
<td>20</td>
</tr>
</tbody>
</table>

\(a\) A mixture of \(E\) and \(Z\) isomers.

The experimental procedure for the addition of an alcohol to trichloroacetonitrile, a modification of the procedure of Cramer,\(^7\) appears to be totally general. For hindered secondary or tertiary alcohols it is more convenient to form the catalytic alkoxide with potassium hydride, and it is essential that the alcohol–alkoxide solution be added to (inverse addition) a solution of trichloroacetonitrile in ethyl ether at 0°.\(^3\) The thermal rearrangement of allylic imidates was first reported by Mumm and Möller\(^8\) in 1937, and has been noted in scattered reports since that time.\(^9\) In these cases the imidates were not available by a general route (as is the case for trichloroacetimidates), and as a result this rearrangement had not become a generally useful synthetic method. Alternative methods for the allylic transposition of oxygen
and nitrogen functions include the thermolysis of allylic sulfamate esters,\textsuperscript{10} phenylurethanes,\textsuperscript{11} oxime O-allyl ethers,\textsuperscript{12} and N-chlorosulfonylurethanes,\textsuperscript{13} as well as the \textit{S}_2' reaction of certain allylic alcohol esters with amines.\textsuperscript{14} These procedures are much less attractive than the method reported here, usually affording mixtures of allylic isomers.\textsuperscript{10,11,12,13,14} Other routes for the preparation of 3,7-dimethyl-1,6-octadien-3-amine have not, to our knowledge, been reported.

\textbf{References and Notes}

1. Department of Chemistry, University of California, Irvine, California, 92717.

\textbf{Appendix}

\textbf{Chemical Abstracts Nomenclature (Collective Index Number); (Registry Number)}

\begin{itemize}
\item silica gel
\item ethanol (64-17-5)
\item potassium carbonate (584-08-7)
\item sulfuric acid (7664-93-9)
\item ethyl acetate (141-78-6)
\item methanol (67-56-1)
\item ether,
\item ethyl ether,
\item diethyl ether (60-29-7)
\item hydrogen (1333-74-0)
\item sodium hydroxide (1310-73-2)
\end{itemize}
oxygen (7782-44-7)
nitrogen (7727-37-9)
toluene (108-88-3)
xylene (106-42-3)
Pentane (109-66-0)
trichloroacetonitrile (545-06-2)
cinnamyl alcohol (104-54-1)
sodium hydride (7646-69-7)
hexane (110-54-3)
geraniol (106-24-1)
2-cyclohexen-1-ol

3,7-DIMETHYL-1,6-OCTADIEN-3-AMINE, 1,6-Octadien-3-amine, 3,7-dimethyl-, linalylamine (59875-02-4)
ceric ammonium nitrate
3-Trichloroacetamido-1-hexene
3-Phenyl-3-trichloroacetamido-1-propene
1-Hepten-3-ol (4938-52-7)
3-Trichloroacetamido-1-cyclohexene
Linalool (78-70-6)
3,5,5-Trimethyl-2-cyclohexen-1-ol
3,5,5-Trimethyl-3-trichloroacetamido-1-cyclohexene
3-(4,4-Ethylendioxybutyl)-2-cyclohexen-1-ol
3-(4,4-Ethylendioxybutyl)-3-trichloroacetamido-1-cyclohexene
potassium hydride (7693-26-7)
(E)-2-Hexen-1-ol (928-95-0)
Geraniol trichloroacetimidate (51479-75-5)
(E)-1-Trichloroacetamido-2-heptene

3,7-Dimethyl-3-trichloroacetamido-1,6-octadiene (51479-78-8)

3,7-Dimethyl-1-trichloroacetamido-2,6-octadiene