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*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.*
PHOTOCHEMICAL RING CONTRACTION OF 2-ETHOXYPYRROLIN-5-ONES TO CYCLOPROPANONE DERIVATIVES: tert-BUTYL N-(1-ETHOXYCYCLOPROPYL) CARBAMATE

[Carbamic acid, (1-ethoxycyclopropyl)-, 1,1-dimethylethyl ester]

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Checked by S. Boettger and M. F. Semmelhack.

1. Procedure

Caution! The photochemical reaction in Part C should be carried out behind a light-absorbent cover or shield. Protective goggles should be worn to avoid exposure of the eyes to ultraviolet light.

A. Succinimide silver salt (Note 1). A 3-l., two-necked, round-bottomed flask equipped with a mechanical stirrer and a pressure-equalizing dropping funnel is charged with a solution of 28.9 g. (0.292 mole) of succinimide (Note 2) in 1.2 l. of absolute ethanol (Note 3). A solution of 48.58 g. (0.2860 mole) of silver nitrate in 200 ml. of dimethyl sulfoxide (Note 4) is added in one portion. The resulting solution is stirred as 700 ml. (0.280 mole) of 0.400 M sodium ethoxide in ethanol (Note 5) and ethanol (Note 6) is added dropwise over 1.5 hours. The off-white silver salt begins to precipitate after ca. 140 ml. of the sodium ethoxide solution has been added. Stirring is continued for 45 minutes after the addition is completed, and the reaction mixture is then stored in a refrigerator at ca. 5° overnight to complete the precipitation and aggregation of the product.

The precipitate is collected on filter paper (Note 7) in a Büchner funnel by vacuum filtration and washed with 100 ml. of absolute ethanol. The solid is slurried in three 75-ml. portions of distilled water (Note 8), 100 ml. of absolute ethanol, two 100-ml. portions of reagent grade acetone, and two 100-ml.
portions of anhydrous ethyl ether. The filter cake is pressed dry in the funnel with suction using a piece of rubber dam, transferred to a tared, 500-ml., round-bottomed flask, and dried under reduced pressure (0.01 mm.) at room temperature for 24 hours (Note 9), yielding 51–54 g. (88–94%) of the silver salt of succinimide.

B. 2-Ethoxypyrrolin-5-one. The flask containing 51–54 g. (0.25–0.26 mole) of succinimide silver salt is equipped with a magnetic stirring bar (Note 10), a heating mantle, and reflux condenser bearing a silica gel drying tube. The solid is suspended in 295 ml. of dry chloroform (Note 11), and 51.4 g. (26.4 ml., 0.330 mole) of ethyl iodide is added in one portion. The flask is covered with aluminum foil, and the mixture is stirred vigorously and heated under reflux for 48 hours. The mixture is cooled, the silver iodide is removed by vacuum filtration through Celite, and the filter cake is washed well with dry chloroform. The filtrate is concentrated by rotary evaporation to a mixture of a dark liquid and a white solid identified as succinimide. Anhydrous diethyl ether is added to dissolve the liquid, and the resulting suspension is filtered through a plug of glass wool, separating 7.7–11.5 g. of succinimide. The ether is removed from the filtrate by rotary evaporation at aspirator pressure, and the residual liquid is distilled under reduced pressure with a short-path distillation apparatus. The product is collected at 74–82° (0.01 mm.) as a faintly yellow oil which crystallizes in the freezer. The yield is 11.5–16.7 g. (32–46% based on sodium ethoxide in Part A) (Note 12) and (Note 13).

C. tert-Butyl N-(1-ethoxycyclopropyl)carbamate. A three-necked, cylindrical irradiation vessel is equipped with a magnetic stirring bar, a water-jacketed quartz immersion well, an inert gas-inlet, and a gas-exit tube connected to a bubbler (Note 14). The vessel is charged with 6.26 g. (0.0493 mole) of redistilled 2-ethoxypyrrolin-5-one (Note 20) and 180 ml. of dry tert-butyl alcohol (Note 15). The solution is stirred and degassed by bubbling nitrogen or argon through the gas-inlet tube for 15 minutes. The degassed solution is stirred and irradiated with ultraviolet light from a 450-watt, Hanovia, medium-pressure, mercury lamp filtered through a Vycor glass sleeve. During the irradiation an atmosphere of nitrogen or argon is maintained, and the lamp is cooled with warm water (35–40°) circulated through the cooling jacket of the immersion well. The progress of the irradiation is monitored by GC (Note 16). When 90% of the 2-ethoxypyrrolin-5-one has reacted, the irradiation is stopped. The solution (Note 17) is transferred to a 250-ml., round-bottomed flask equipped with a magnetic stirring bar and an air-cooled reflux condenser mounted with a T-shaped nitrogen inlet. Nitrogen is passed through the apparatus for 30 minutes, after which the solution is stirred and heated at reflux under a nitrogen atmosphere for 20 hours (Note 18). The solvent is removed by rotary evaporation, and the residual orange oil is refrigerated to induce crystallization. Sublimation of the solid at 35–40° (0.05 mm.) affords 5.5–6.3 g. (56–64%) of the carbamate as white needles, m.p. 38–40° (Note 19) and (Note 20).

2. Notes

1. In parts A and B care should be taken to minimize the exposure of silver-containing reactants and products to light.
2. Succinimide purchased from MC and B Manufacturing Chemists was used without purification.
3. Absolute ethanol from a commercial supplier was used.
4. A mixture of silver nitrate and dimethyl sulfoxide was stirred vigorously for ca. 1 hour to dissolve all of the salt. Reagent grade dimethyl sulfoxide was used without purification.
5. The sodium ethoxide solution was prepared from the reaction of 9.2 g. (0.40 mole) of sodium with 1 l. of absolute ethanol and is standardized by titration with aqueous 0.1 N hydrochloric acid. The appropriate volume of the solution to give 0.280 mole of base was used.
6. Slightly less than equivalent amounts of both silver nitrate and sodium ethoxide are used to minimize the formation of silver oxide which imparts a brown color to the product.
7. The submitters state that the use of a sintered-glass funnel may cause discoloration of the product. However, the checkers used a sintered glass funnel in one run with no adverse effect on the yield or purity of the product.
8. A considerable amount of sodium nitrate is present in the precipitate. Although the presence of sodium nitrate did not hinder small-scale alkylation reactions (ca. 250 mg.), the submitters recommend that it be removed in larger runs to facilitate the isolation and drying of the silver salt. These washings are most easily done without removing the material from the filter. However, the solid must be slurried thoroughly in each portion of solvent, particularly with acetone and ether. Care must be
The irradiation vessel used by the submitters were approximately 35 cm. and 6.2 cm., respectively. Two short necks with protons, assignment): 1.4 (t, \(J = 7\), 3H, \(\text{OCH}_2\text{C}_2\text{H}_2\)), 2.4–3.0 (m, 4H, \(\text{CH}_2\text{C}_2\text{H}_2\)), 4.45 (q, \(J = 7\), 2H, \(\text{OCH}_2\text{C}_2\text{H}_2\)); UV (cyclohexane) nm. max. (\(\epsilon\)): 273 (55).

14. The irradiation apparatus was similar to one depicted in the procedure for bicyclo[2.1.0]pent-2-ene in \textit{Org. Synth.}, \textbf{Coll. Vol. 6}, 145 (1988), Figure 2, Section A. The height and inside diameter of the irradiation vessel used by the submitters were approximately 35 cm. and 6.2 cm., respectively. Two short necks with \(T\) 14/20 outer joints were located on the shoulder of the vessel just below the \(T\) 60/50 center joint. One neck was capped with a rubber septum and the other was connected to the exit bubbler. The nitrogen inlet was a syringe needle passing through the septum and connected to a section of Teflon tubing that extended to the bottom of the vessel. The checkers used a similar 23 × 7.5 cm. irradiation vessel that had a fritted-glass inlet for argon situated at the base as shown in the figure referred to above. The solution was agitated during the irradiation by a continual flow of argon rather than by magnetic stirring.

The apparatus is dried in an oven at 140° overnight and cooled under nitrogen or argon prior to the irradiation. A Vycor filter sleeve and a 450-watt, medium-pressure mercury lamp are placed in the immersion well. The Vycor filter, the quartz immersion well (catalog No. 19434), the 450-watt mercury lamp (catalog No. 679A36), and the requisite transformer are all available from Hanovia Lamp Division, Canrad-Hanovia Inc., 100 Chestnut Street, Newark, New Jersey 07105.

15. Reagent grade tert-butyl alcohol was distilled from calcium hydride prior to use. The scale described is that used by the checkers. The submitters irradiated 4.0 g. (0.032 mole) of 2-ethoxypryrrolin-5-one in 115 ml. of dry tert-butyl alcohol.

16. The submitters used a 2.1 m. × 0.64 cm. column with 5% fluoro silicone (FS-1265) supported on Ditaopor S as stationary phase. With a column temperature of 170° and a helium flow rate of 60 ml. per minute, 2-ethoxypryrrolin-5-one has a retention time of 2.2 minutes. The analysis was carried out at 160° by the checkers, using a column of 5% diethylene glycol succinate–Bentone\(^{34}\) supported on Ditaopor S. The starting material had a retention time of 3.9 minutes under these conditions. Bentone\(^{34}\) is available from Applied Sciences Laboratory, Box 440, State College, Pennsylvania 16801.

17. At this point the product consisted mostly of the isocyanate, since the reaction with tert-butyl alcohol is relatively slow at 35–40°. If the photolysis is carried out in an aprotic solvent such as tetrahydrofuran, the isocyanate may be isolated.\(^2\) However, care must be exercised to avoid losses of this rather volatile and moisture-sensitive compound.

18. The isocyanate is completely consumed at this time, as evidenced by the disappearance of the absorption band at 2250 cm.\(^{-1}\) in the IR spectrum.
succinimide. With 2-ethoxypyrrolin-5-one purified by a single distillation, the product was obtained as a gummy solid that was difficult to purify. Nevertheless, the IR and $^1$H NMR spectra of this material were essentially identical to those of pure tert-butyl N-(1-ethoxycyclopropyl)carbamate. The submitters obtained 4.4–4.8 g. (70–76%) of carbamate, m.p. 40–42°, from 4.0 g. of 2-ethoxypyrrolin-5-one. The product has the following spectral characteristics: IR (neat) cm$^{-1}$: 3333, 2940, 1754 (C=O); $^1$H NMR (CDCl$_3$), δ (multiplicity, coupling constant $J$ in Hz., number of protons, assignment): 0.80–1.15 (m, 4H, cyclopropyl H), 1.13 (t, $J$ = 7, 3H, OCH$_2$CH$_3$), 1.47 [s, 9H, C(CH$_3$)$_3$], 3.68 (q, $J$ = 7, 2H, OCH$_2$CH$_3$), 5.75 (broad, 1H, NH).

3. Discussion

The procedure described here for the preparation of succinimide silver salt is a modification of one reported for the formation of the silver derivative of maleimide. The alkylation step is modeled after the procedure of Comstock and Wheeler, who prepared 2-ethoxypyrrolin-5-one in unspecified yield, and is an improvement over a later procedure developed in the laboratories of the submitters. The general scheme has been successfully applied to the preparation of a variety of 2-ethoxypyrrolin-5-ones (Table I) as well as 6-ethoxy- and 6-propoxy-4,5-dihydro-2(3H)-pyridone from the corresponding five- and six-membered cyclic imides.

The photochemical rearrangement of substituted 2-ethoxypyrrolin-5-ones is a general reaction of synthetic utility and high stereoselectivity, which affords the corresponding 1-ethoxycyclopropyl isocyanates and their derivatives in useful yields (Table I). The procedure reported here is the only known preparation of tert-butyl N-(1-ethoxycyclopropyl)carbamate, a precursor of 1-aminocyclopropanol and 1-ethoxycyclopropylamine. 1-Aminocyclopropanol has previously been prepared in low yield by the addition of ammonia to cyclopropanone. The photorearrangement of 2-ethoxypyrrolin-5-one to tert-butyl N-(1-ethoxycyclopropyl)carbamate followed by hydrolysis to 1-aminocyclopropanol is a key step in the synthesis of the alkaloid coprine. Cyclopropanone derivatives have been used as precursors for a variety of compounds such as β-lactams, cyclobutanones, and cyclopropanols.

<table>
<thead>
<tr>
<th>2-Ethoxypyrrolin-5-one</th>
<th>Yield (%)</th>
<th>Photoproduct or Its Derivative</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>2-Ethoxypyrrolin-5-one</td>
<td>46$^a$</td>
<td>OCN(CH$_3$)$_2$NHN(C$_2$H$_5$)</td>
<td>43$^b$</td>
</tr>
<tr>
<td></td>
<td>59</td>
<td>N=C=OOC$_2$H$_5$</td>
<td>76$^b$</td>
</tr>
<tr>
<td></td>
<td>89</td>
<td>N=C=OOC$_2$H$_5$</td>
<td>64$^b$</td>
</tr>
<tr>
<td></td>
<td>74</td>
<td>N=C=OOC$_2$H$_5$</td>
<td>53$^b$</td>
</tr>
</tbody>
</table>

TABLE I
PREPARATION AND IRRADIATION OF 2-ETHOXYPYRROLIN-5-ONES
2-Ethoxypyrrolin-5-one reacts with secondary amines, giving 2-aminopyrrolin-5-ones which photochemically rearrange to aminocyclopentyl isocyanates in 80–90% yield.\textsuperscript{13} Furthermore, 1,4-bis[(pyrrolin-3-onyl)methylamino]-2-butyne photorearranges to 1,4-bis[(isocyanatocyclopropyl)methylamino]-2-butyne. This reaction is of potential use for photocrosslinking polyurethanes and polyureas.

\begin{figure}[h]
\centering
\includegraphics[width=0.5\textwidth]{reaction_diagram.png}
\caption{Photocrosslinking reaction}
\end{figure}

\begin{flushright}
R = Me
\end{flushright}

\textsuperscript{a}The yield was 84% based on unrecovered imide.
\textsuperscript{b}The product is a mixture of endo- and exo- isomers.
\textsuperscript{c}The isomers were separated by preparative GC.
\textsuperscript{d}The product is a mixture of cis- and trans- isomers.

References and Notes

1. Chemistry Department, University of Colorado, Boulder, Colorado 80309.
Appendix

Chemical Abstracts Nomenclature (Collective Index Number);
(Registry Number)

6-ethoxy- and 6-propoxy-4,5-dihydro-2(3H)-pyridone

Bentone$^{34}$

ethanol (64-17-5)

hydrochloric acid (7647-01-0)

ammonia (7664-41-7)

ether,
ethyl ether,
diethyl ether (60-29-7)

chloroform (67-66-3)

silver oxide (20667-12-3)

silver nitrate (7761-88-8)

nitrogen (7727-37-9)

aluminum (7429-90-5)

acetone (67-64-1)

sodium (13966-32-0)

sodium ethoxide (141-52-6)

sodium nitrate

Succinimide (123-56-8)

Ethyl iodide (75-03-6)

Tetrahydrofuran (109-99-9)

dimethyl sulfoxide (67-68-5)

argon (7440-37-1)

tert-butyl alcohol (75-65-0)

silver iodide (7783-96-2)
calcium hydride (7789-78-8)

helium (7440-59-7)

diethylene glycol succinate

Bicyclo[2.1.0]pent-2-ene (5164-35-2)

CYCLOPROPANONE (5009-27-8)

Carbamic acid, (1-ethoxycyclopropyl)-, 1,1-dimethylethyl ester, tert-Butyl N-(1-ethoxycyclopropyl)carbamate (28750-48-3)

Succinimide silver salt, silver salt of succinimide

2-Ethoxypyrrolin-5-one (29473-56-1)

1-aminocyclopropanol

1-ethoxycyclopropylamine

1,4-bis[(pyrrolin-3-onyl)methylamino]-2-butyne

1,4-bis[(isocyanatoxytocyclopropyl)methylamino]-2-butyne

N-ethylsuccinimide (2314-78-5)

silver salt of isatin

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