# Alkylations of Vinylogous Amides, Vinylogous Esters and Vinylogous Thioesters with Potassium Hydride

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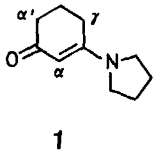
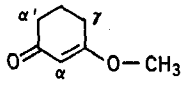
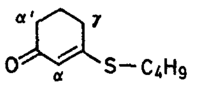
In recent communications it has been shown that the lithium enolate of vinylogous amides[1,2], vinylogous esters[3], and vinylogous thioesters[4] generated *via* lithium diisopropylamide resulted in $\gamma$ or $\alpha'$ alkylated products in good yield. In addition, evidence has been gathered that indicates the $\alpha'$ alkylation products of vinylogous ester **2** and thioester **3** are obtained from reaction of the kinetically formed enolate (generated using excess base), whereas the $\gamma$ product of vinylogous amide **1** results from alkylation of an equilibrated (thermodynamic) enolate[5] (slightly less than one equivalent of base employed)[2,11]. Described herein are the results obtained when the potassium enolate, generated from potassium hydride[6], of the aforementioned systems were treated with various alkylating agents. The results of several such experiments are tabulated in the Table.



**1**

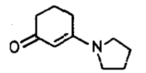
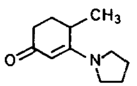
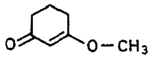
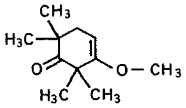
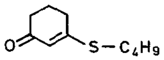
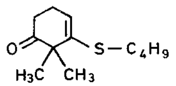
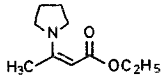
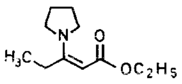
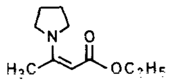
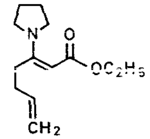
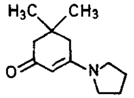
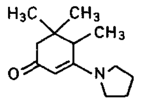
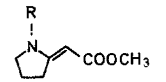
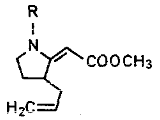


**2**



**3**

**Table.** Alkylations[a] of Vinylogous Amides, Vinylogous Esters, and Vinylogous Thioesters with Methyl Iodide and 1-Bromopropene using two Equivalents of Potassium Hydride

| Substrate | | Alkylating agent | Product[b] | | m.p. or b.p./torr[c] | Yield (%)[d] | | I.R.[e] | $\nu$ cm$^{-1}$ | $^1$H-N.M.R. | (CDCl$_3$/TMS) |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | A | B | (>C=O) | (>C=C<) | H$_{vinyl}$ | $\delta$ ppm —CH$_3$ |
| **1** |  | H$_3$C—J | **4** |  | 93–94° | 40–60 | 84–90[f] | 1600 | 1550 | 4.88 (s) | 1.26 (d) |
| **2** |  | H$_3$C—J | **5** |  | 150–155°/1.8 | – | 8[g] | 1710 | 1680 | 4.66 (t) | 1.13 (s), 1.22 (s) |
| **3** |  | H$_3$C—J | **6** |  | 160°/1.8 | 50 | 50[h] | 1720 | 1620 | 5.50 (broad) | 1.34 (s) |
| **7** |  | H$_3$C—J | **8** |  | 134–138°/0.25 | 52 | 82[i] | 1690 | 1590 | 4.40 | 1.15 (t) |
| **7** |  | Br—CH$_2$—CH=CH$_2$ | **9** |  | 160–162°/0.25 | – | 83[i] | 1690 | 1590 | 4.40 | – |
| **10** |  | H$_3$C—J | **11** |  | 111–112° (ether) | 40 | 65 | 1600 | 1550 | 4.91 | 1.18 (d) |
| **12** |  | Br—CH$_2$—CH=CH$_2$ | **13** |  | 200°/0.05 | 30–40 | 35[i] | 1680 | 1600 | 4.60 | – |

[a] These enolates were formed by either stirring the starting material with potassium hydride for five hours at room temperature or refluxing the mixture for one hour.

[b] The spectral and analytical data (C ±0.30%, H ±0.30%) for all new compounds reported are consistent with the structures proposed.

[c] Boiling points reported are oven temperatures observed for bulb to bulb distillation.

[d] Reported yields refer to isolated products; Method A using lithium diisopropylamide, method B using potassium hydride.

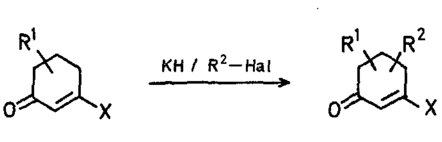
[e] Liquids measured as films, solids in CHCl$_3$ solution.

[f] Isolated via preparative thin layer chromatography (silica gel, 10% methanol/ether); 60% yield with 1 equiv of potassium hydride.

[g] Isolated via column chromatography (silica gel, 20% pentane/ether).

[h] Isolated via column chromatography (silica gel, 50% pentane/ether); 25% yield with 1.5 equiv. of potassium hydride.

[i] Isolated via bulb to bulb distillation.



**1-3, 10** **4-6, 11**

Typically, 3-pyrrolidino-2-cyclohexen-1-one (**1**, 1 equiv) was added to potassium hydride[7,8] ( ~ 2 equiv) in tetrahydrofuran (0°) followed by addition of methyl iodide (1 equiv) yielding 4-methyl-3-pyrrolidino-2-cyclohexen-1-one (**4**, $\gamma$-alkylation, 84 to 90%). The presence of $\alpha'$-alkylated product (5%) is indicative of incomplete equilibration of the initially formed (cross conjugated) enolate. In cases where 2 equivalents of methyl iodide were used varying amounts of $\gamma$-dialkylation resulted. These results should be compared to the 40–60% yields of $\gamma$-alkylation reported earlier using the lithium enolate of **1** which is best generated with lithium diisopropylamide in hexamethylphosphoric triamide/tetrahydrofuran mixtures with reaction times of twenty hours at room temperature followed by three hours at 40–50° prior to alkylation.

In contrast to these results are the potassium hydride alkylations of **2** and **3**. Addition of 3-methoxy-2-cyclohexen-1-one (**2**, 1 equiv) to potassium hydride (2 equiv) in tetrahydrofuran (0°), as described above, did not result in simple $\gamma$ or $\alpha'$ carbanion alkylation but rather afforded polyalkylation with tetramethyl ketone **5** as the major product suggestive of a reaction proceeding *via* an equilibrating process. 3-Butylthio-2-cyclohexen-1-one (**3**, 1 equiv) under these same conditions resulted in $\alpha$-dialkylation (**6**), with little $\alpha'$ product from alkylation of the kinetic enolate[9]. In an analogous fashion the lithium enolate of **3**, in the presence of hexamethylphosphoric triamide with extended reaction time periods, also leads to **6** in approximately 50% yield.

While the potassium enolates of systems, **1**, **2**, and **3** are readily generated at 0°, yields of mono($\gamma$) alkylated products of enamino esters are maximized by generating the appropriate enolate in refluxing tetrahydrofuran. For example, ethyl 3-pyrrolidino-2-butenoate (**7**, 1 equiv) was added to potassium hydride ( ~ 2 equiv) in tetrahydrofuran at 25° and heated under reflux for one hour. The reaction mixture was cooled (0°), methyl iodide (1.2 equiv) added, and then refluxed for an additional hour. Standard purification techniques afforded ethyl 3-pyrrolidino-2-pentenoate **8** in 82% yield. Similarly, methyl *N*-(3,4-dimethoxyphenethyl)-$\alpha$-tetrahydropyrrolidinylideneacetate **12** formed $\gamma$-substituted enaminoester **13** using potassium hydride and allyl bromide.

Potassium hydride offers several advantages over lithium diisopropylamide in effecting the alkylation of enaminoketones and esters as described above. First, more convenient reaction temperatures and much shorter reaction times are necessary for this potassium enolate formation. Secondly, realization of increased yields of alkylated enaminoesters and ketones makes this method synthetically useful. Finally, the use of hexamethylphosphoric triamide, recently shown to be carcinogenic[10], is precluded.

The synthetic potential of $\alpha'$-alkylations using the lithium enolates of vinylogous ester **2** and thioester **3** is complemented by the convenient $\gamma$-alkylation of enaminoketones and esters **7** and **12** employing potassium hydride. Using potassium hydride, monoalkylation of thioester **3** and enol ether **2** are not as synthetically useful as those of enamino ketone **1**. However, realization of products resulting from an alternate (equilibrated enolate) alkylation process not previously reported for systems **2** and **3** must be considered when such compounds are incorporated into a synthetic plan. Further results concerning the reactivity of the lithium and potassium enolate of **1**, **2**, and **3** and evidence as to the mechanism of potassium enolate equilibration will be forthcoming.

**General Procedure for Potassium Hydride Induced Alkylations:** To a solution of potassium hydride (2 mol-equiv) in tetrahydrofuran at 0° was added the appropriate $\beta$-substituted-2-cyclohexen-1-one (1 mol-equiv) with stirring under nitrogen. This mixture was stirred for an additional 5 h at room temperature. The reaction was cooled to 0° and methyl iodide (1 mol-equiv) slowly added. The reaction was stirred for an additional 12 h at room temperature, carefully quenched with water and extracted using ether. The ether phases were dried ($MgSO_4$), concentrated in vacuo and the products isolated by distillation or chromatography (column or T.L.C.) on silica gel (see Table).

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[2] J. E. Telschow, W. Reusch, *J. Org. Chem.* **40**, 862 (1975).

[3] G. Stork, R. L. Danheiser, B. Ganem, *J. Am. Chem. Soc.* **95**, 3414 (1973).

[4] R. B. Gammill, T. A. Bryson, *Tetrahedron Lett.* **1975**, 3793.

[5] R. L. Cargill, T. E. Jackson, *J. Org. Chem.* **38**, 2125 (1973).

[6] C. A. Brown, *J. Org. Chem.* **39**, 3913 (1974).

[7] Removal of the oil dispension prior to alkylation simplifies isolation procedure, however, the presence of the oil is not detrimental to the reaction.

[8] We have not observed any advantage in the use of potassium amide generated as outlined by Brown (see Ref. 6) in the course of our studies.

[9] In several reactions less than 1% of 2,2-dimethyl-6-methyl-3-thiobutyl-2-cyclohexen-1-one was present (b.p. 122°/0.125 torr).

[10] *Chem. Eng. News*, September 29, p. 17, (1975).

[11] Unpublished studies now underway in this laboratory are generating evidence that supports this proposition as does the evidence in ref. 2.