Tetrahedron Letters Vol. 21, pp 3385 - 3388
©Pergamon Press Ltd. 1980. Printed in Great Britain

0040-4039/80/0822-3385$02.00/0

# REDUCTION WITH ORGANIC SELENIUM COMPOUNDS II.

## REDUCTION OF SCHIFF BASES WITH SELENOPHENOL

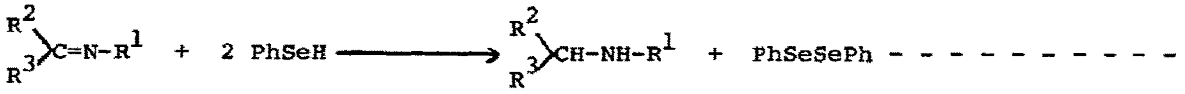
## REDUCTIVE ALKYLATION OF AMINES WITH CARBONYL COMPOUNDS

Ken Fujimori, Hiroshi Yoshimoto and Shigeru Oae*

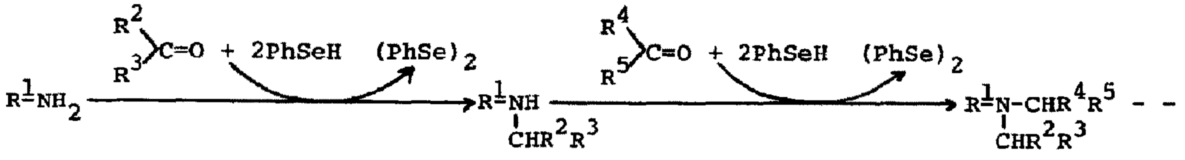
Department of Chemistry, The University of Tsukuba, Sakura-mura, Ibaraki 305 Japan

Reduction of Schiff bases with selenophenol proceeded at room temperature to yield the corresponding sec. amines quantitatively. The reaction of either prim. amine or sec. amine with carbonyl compound and selenophenol gave sec. or tert. amines, respectively. Different alkyl groups can be introduced successively on nitrogen of prim. amines to afford tert. amines bearing three different alkyl groups desired by one pot reaction.

In the previous communication we reported that selenophenol is an excellent reagent for reductive cleavage of N=N, N=O, N-N and N-O bonds under mild conditions.[1) We have found that selenophenol is also an excellent reagent not only for reduction of Schiff bases but also for reductive alkylation of amines with carbonyl compounds, as shown in the following equations, (1) and (2).



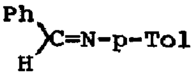
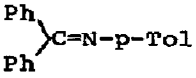
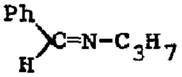
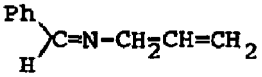
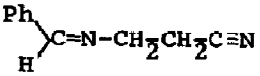
$$\mathrm{R^2R^3C{=}N{-}R^1} + 2\,\mathrm{PhSeH} \longrightarrow \mathrm{R^2R^3CH{-}NH{-}R^1} + \mathrm{PhSeSePh} \quad - - - - - - - - - - \quad (1)$$



$$\mathrm{R^1{-}NH_2} \xrightarrow{\mathrm{R^2R^3C{=}O} + 2\mathrm{PhSeH} \rightarrow \mathrm{(PhSe)_2}} \mathrm{R^1{-}NH(CHR^2R^3)} \xrightarrow{\mathrm{R^4R^5C{=}O} + 2\mathrm{PhSeH} \rightarrow \mathrm{(PhSe)_2}} \mathrm{R^1{-}N(CHR^4R^5)(CHR^2R^3)} \quad - - \quad (2)$$

There are several known methods to reduce Schiff bases and also for reductive alkylation of amines with carbonyl compounds, i.e., catalytic hydrogenation[2) and reduction with formic acid,[3) formamide,[3) borane,[4)

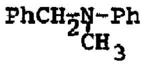
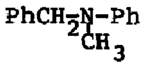
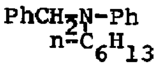
Table 1. Reduction of Schiff Bases with Selenophenol at Room Temperature

| Substrate | PhSeH[a)] | Solvent | Time(min) | Product Amine | Isolated Yield(%) |
|---|---|---|---|---|---|
|  $\mathrm{{}^{Ph}_{H}{>}C{=}N\text{-}p\text{-}Tol}$ | 2.5 | $CH_3CN$ | 10 | $\mathrm{PhCH_2NH\text{-}p\text{-}Tol}$ | 91 |
| " | 2.5 | $Et_2O$ | 10 | " | 91 |
| " | 2.5 | $CHCl_3$ | 10 | " | 95 |
|  $\mathrm{{}^{Ph}_{Ph}{>}C{=}N\text{-}p\text{-}Tol}$ | 2.5 | $CHCl_3$ | 10 | $\mathrm{Ph_2CH\text{-}NH\text{-}p\text{-}Tol}$ | 77 |
|  $\mathrm{{}^{Ph}_{H}{>}C{=}N\text{-}C_3H_7}$ | 3 | $Et_2O$ | 10 | $\mathrm{PhCH_2NH\text{-}C_3H_7}$ | 89 |
|  $\mathrm{{}^{Ph}_{H}{>}C{=}N\text{-}CH_2CH{=}CH_2}$ | 2.5 | $CHCl_3$ | 10 | $\mathrm{PhCH_2NH\text{-}CH_2CH{=}CH_2}$ | 83 |
|  $\mathrm{{}^{Ph}_{H}{>}C{=}N\text{-}CH_2CH_2C{\equiv}N}$ | 2.5 | $CHCl_3$ | 10 | $\mathrm{PhCH_2NH\text{-}CH_2CH_2C{\equiv}N}$ | 80 |

a) Mole ratio to substrate.

borane-pyridine complex,[5)] $NaBH_4$,[6)] $LiAlH_4$,[7)] $NaBH_3CN$[8)] and $Fe(CO)_4H$.[9)] Each method has its own merit and shortcoming, i.e., some require drastic conditions and some are less selective. Our new method has following four advantages. 1) The reaction proceeds quantitatively at room temperature. 2) The selectivi of the reagent is different from the reagents hitherto known, e.g. selenophenol does not react with C≡N, C=C, $-\overset{\mathrm{O}}{\overset{\|}{\mathrm{C}}}\text{-NH-}$ and $-CO_2R$ groups under the reaction condition applied in this work. 3) Simple mixing of reagent and the substrate under argon atmosphere without any pH control is enough to complete the reactio and the amines formed can be easily separated from the neutral diselenide and some excess selenophenol. 4) The N-alkylation of both primary and secondary

Table 2. Reductive Alkylation of Amines with Carbonyl Compounds promoted by Selenophenol at Room Temperature.

| Starting Material Carbonyl Compound | Starting Material Amine | Solvent | Time(min) | Product Amine | Isolated Yield(%) |
|---|---|---|---|---|---|
| PhCH=O | p-TolNH$_2$ | CHCl$_3$ | 30 | PhCH$_2$NH-p-Tol | 92 |
| PhCH=O | PhCH$_2$NH$_2$ | Et$_2$O | 10 | (PhCH$_2$)$_2$NH | 87 |
| PhCH=O | CH$_2$=CH-CH$_2$NH$_2$ | Et$_2$O | 10 | PhCH$_2$NH-CH$_2$CH=CH$_2$ | 92 |
| PhCH=O | N≡C-CH$_2$CH$_2$NH$_2$ | Et$_2$O | 10 | PhCH$_2$NH-CH$_2$CH$_2$C≡N | 86 |
| n-PrCH=O | PhCH$_2$NH$_2$ | CHCl$_3$ | 60 | n-Bu-NH-CH$_2$Ph | 86 |
| PhCH=O | Ph-NH-CH$_3$ | CHCl$_3$ | 60 |  $PhCH_2\underset{CH_3}{N}\text{-}Ph$ | 91 |
| 2 PhCH=O | PhCH$_2$NH$_2$ | CHCl$_3$ | 60 | (PhCH$_2$)$_3$N | 93[a] |
| 1)PhCH=O<br>2)HCH=O[c] | Ph-NH$_2$ | CHCl$_3$ | 10<br>180 |  $PhCH_2\underset{CH_3}{N}\text{-}Ph$ | 80[b] |
| 1)PhCH=O<br>2)n-C$_5$H$_{11}$CH=O | PhNH$_2$ | CHCl$_3$ | 10<br>360 |  $PhCH_2\underset{n\text{-}C_6H_{13}}{N}\text{-}Ph$ | 81[d] |

a) [PhCH=O]:[PhCH$_2$NH$_2$]:[PhSeH]= 2 : 1 : 4.5 (mole ratio).

b) [PhCH=O]:[Ph-NH$_2$]:[PhSeH]:[HCH=O]= 1 : 1 : 5 :ca.2 (mole ratio).

c) 35% Formalin was used.

d) [PhCH=O]:[Ph-NH$_2$]:[PhSeH]:[n-C$_5$H$_{11}$CH=O]= 1 : 1 : 5 : 1.2 (mole ratio).

amines proceeds smoothly to give secondary and tertiary amines, respectively. Primary amines can be converted to secondary or tertiary amines by controlling the amounts of the reagents. On the other hand, an introduction of two different alkyl groups on the nitrogen of primary amines is conducted by successive addition of alkylating agents, carbonyl compounds, as one pot reaction in the presence of 4.5 equivalent selenophenol affording tertiary amines bearing three different substituents desired to be introduced. Chloroform was found to be the most suitable solvent for this reaction among a few solvents examined including acetonitrile, ether, methanol and chloroform. Sometimes crystalline complexes of selenophenol with either the starting or the product amines were precipitate out from the chloroform solution. In such cases a small amount of methanol to dissolve the complex was added.

A typical procedure is as follows. A solution of N-benzylidene-p-toluidi (1 mmol) or a mixture of benzaldehyde(1 mmol) and p-toluidine(1 mmol) in 1 ml of $CHCl_3$ was placed in a reaction vesel with a serum cap under argon atmosphere. Then 2.5 mmol of selenophenol was added through serum cap by injection at room temperature. The mixture was allowed to stand for 10 min. The solvent was evaporated and the residure was treated by ether - dil. aqueous NaOH solution. An organic layer was extracted by dil. HCl. Diphenyl diselenide was recovered from the organic layer. Acidic solution was neutrallized by $NaHCO_3$and extract with ether. Ether extracts contain almost pure N-benzyl-p-toluidine which was then purified by column chromatography to give pure amine 187.4 mg, 95%. The results of reduction of Schiff bases are listed in Table 1. Table 2 summarizes the data of the reductive alkylation of amines with carbonyl compoun by treatment with selenophenol.

## References

1) K. Fujimori, H. Yoshimoto and S. Oae, Tetrahedron Lett., 4397 (1979).
2) W. S. Emerson, Org. Reactions vol. 4, Chap. 3, John Wiley Sons, Inc., New York (1949).
3) M. L. Moor, ibid., vol. 5, Chap. 7 (1949).
4) H. Feuer and B. F. Vincent, J. Org. Chem., 30, 2877 (1965).
5) M. Kawase and Y. Kikugawa, J. Chem. Soc. Perkin Trans. I, 643 (1979).
6) Y. Kikugawa, S. Ikegami and S. Yamada, Chem. Pherm. Bull.(Tokyo), 17, 98 (1969).
7) W. G. Brown, Org. Reactions vol. 6, Chap. 10 (1951).
8) R. F. Borch, M. D. Bernstein and H. D. Durst, J. Amer. Chem. Soc., 93, 2897 (1971).
9) Y. Watanabe, S. C. Shim, T. Mitsudo, M. Yamashita and Y. Takegami, Bull. Chem. Soc. Japan, 49, 1378 (1976).

(Received in Japan 24 May 1980)