Tetrahedron Letters,Vol.26,No.35,pp 4183-4186,1985 0040-4039/85 $3.00 + .00
Printed in Great Britain

AN IMPROVED PROCEDURE FOR THE CONVERSION OF INDOLINES INTO INDOLES

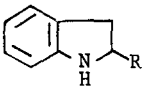
Ichiya Ninomiya, Toshiko Kiguchi and Chiyomi Hashimoto
Kobe Women's College of Pharmacy, Motoyamakita, Higashinada,
Kobe 658, Japan

and

Derek H.R. Barton, Xavier Lusinchi and Pierre Milliet
Institut de Chimie des Substances Naturelles, C.N.R.S.,
91190 Gif-sur-Yvette, France

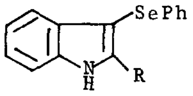
Abstract - The addition of a sacrificial enamine (such as indole), or of a vinyl ether (like dihydropyran) to an indoline during dehydrogenation by phenylseleninic anhydride dramatically improves the yield of the corresponding indole. This is due to scavenging of Se^{II} phenylselenenating species.

The total synthesis of the ergoline nucleus[1a] remains a topic of current importance and interest.[1b] Often the synthetic route adopted passes at the end of the synthesis by the dehydrogenation of an indoline into the corresponding indole. The yields are often mediocre.[2] The use of phenylseleninic anhydride, which is an efficient reagent for the dehydrogenation of secondary amines, can give improved yields.[3] However, with 3-substituted indolines far from quantitative yields were obtained. On the other hand indoline itself 1, or 2-methylindoline 2, gave quantitative dehydrogenation. The indoles produced then reacted immediately with a Se^{II} species (such as PhSeOH) to give the 3-phenylselenated species 3 and 4. 3-Methylindoline 5 gave a lower yield of 3-methylindole 6, which was more slowly converted[3b] into the phenylseleno derivative 7.



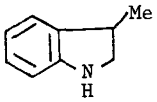
1 R = H

2 R = Me

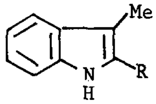


3 R = H

4 R = Me



5



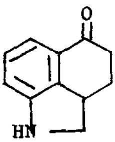
6 R = H

7 R = SePh

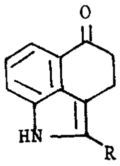
It seemed to us[3b] that the phenylseleninic anhydride was effecting dehydrogenation efficiently and that the product of elimination (PhSeOH) was responsible for those yields which were unsatisfactory. Clearly the addition of a sacrificial enamine (scavenger) to trap the Se^{II} reagent should allow a better yield of the desired indole. Clearly indole itself was a compound which should have the correct reactivity and should protect more complicated indole derivatives from functionalisation by Se^{II}. Another compound examined was dihydropyran which was an efficient reagent for trapping sulphenic acids in the penicillin series.[4]

The results for the dehydrogenation of the indole[5] 8 into Uhle's ketone[6] 9 are shown in the Table and demonstrate that the theoretical hypothesis is correct.

The comparison of entries 2 and 6 is particularly instructive. In the absence of indole the mass balance is deficient by 38% and 9 is contaminated with a significant amount of 10.[7] In the presence of indole the mass balance is nearly perfect and only Uhle's ketone 9 is formed.



8



9 R = H

10 R = SePh

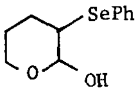
Table[a]

Entry	Scavenger: (Equivs.)	Temp. (°C)	Time (hrs)	Isolated Yields (%) 9	10	Yields of 3 or 11 (%)
1	None	R.T.[b]	2	57	-	-
2	None	50-60	5.5	42	20	-
3	Indole (1)	R.T.	23	90	-	3 (quant.)
4	Indole (2)	R.T.	23	95	-	3 (quant.)
5	Indole (3)	R.T.	23	92	-	3 (quant.)
6	Indole (3)	50-60	2	98	-	3 (quant.)
7	Dihydropyran (3)	R.T.	23	96	3.3	11 (25)
8	Dihydropyran (3)	50-60	3	91	3.5	11 (34)

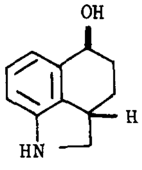
a. The derivative 8 and indole in tetrahydrofuran (5 ml for 0.37 mmol of 8) was added to 0.5 M equiv. of phenylseleninic anhydride.
b. Room temperature.

Dihydropyran can equally be used as scavenger (giving 11)[8], but it is slightly less efficient than indole and gives trace amounts of 10.

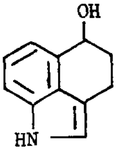
Similarly satisfactory results have been obtained using the alcohol[5] 12. At room temperature with 3 equivalents of indole a 96% yield of 13, m.p. 125-126° was obtained[8] after 23 hrs with a quantitative formation of 3. A small amount (1.7%) of 9 was isolated. Similarly at 50-60° in 2 hrs the yield of 13 was 64%, whilst 13% of 9 was obtained. The relatively facile oxidation of benzylic alcohols has precedent[9].



11



12



13

References

1. a) E.C. Kornfeld, E.J. Fornefeld, G.B. Kline, M.J. Mann, D.E. Morrison, R.G. Jones and R.B. Woodward, J. Am. Chem. Soc., 78, 3087 (1956); E.C. Kornfeld and N.J. Bach, Chem. Ind., 1233 (1971); M. Julia, F. Le Goffic, J. Igolen and M. Baillarge, Tetrahedron Lett., 1569 (1969); I. Ninomiya, T. Kiguchi and T. Naito, J. Chem. Soc., Perkin Trans. 1, 208 (1980); b) M. Natsume and H. Muratake, Heterocycles, 16, 357 (1981); 16, 1481 (1981); R. Ramage, V.W. Armstrong and S. Coulton, Tetrahedron, 37, Suppl. 1, 157 (1981); W. Oppolzer, E. Francotte and K. Bättig, Helv. Chim. Acta, 64, 478 (1981); W. Oppolzer, J.I. Grayson, H. Wegmann and M. Urrea, Tetrahedron, 39, 3695 (1983); T. Kiguchi, C. Hashimoto, T. Naito and I. Ninomiya, Heterocycles, 19, 2279 (1982); T. Kiguchi, C. Hashimoto and I. Ninomiya, ibid., 22, 43 (1984); I. Ninomiya, C. Hashimoto and T. Kiguchi, ibid., 22, 1035 (1984); T. Kiguchi, C. Hashimoto and I. Ninomiya, ibid., 23, 1377 (1985); T. Kiguchi, C. Hashimoto and I. Ninomiya, ibid., in press; J. Rebek, D.F. Tai and Y.-K. Shu, J. Am. Chem. Soc., 106, 1813 (1984); A.P. Kozikowski and P.D. Stein, J. Am. Chem. Soc., 107, 2569 (1985); for reviews see: D.C. Horwell, Tetrahedron, 36, 3123 (1980); A.P. Kozikowski, Heterocycles, 16, 267 (1981).
2. R.J. Sundberg, "The Chemistry of Indoles", Academic Press, New York, p. 132, 1970; A. Inada, Y. Nakamura and Y. Morita, Chem. Lett., 1287 (1980); M. Kawase, Y. Miyake and Y. Kikugawa, J. Chem. Soc., Perkin Trans. 1, 1401 (1984).
3. a) D.H.R. Barton, X. Lusinchi and P. Milliet, Tetrahedron Lett., 23, 4949 (1982); b) D.H.R. Barton, X. Lusinchi and P. Milliet, Tetrahedron, in press.
4. D.H.R. Barton, D.G.T. Greig, G. Lucente, P.G. Sammes, M.V. Taylor, C.M. Cooper, G. Hewitt and W.G.E. Underwood, Chem. Commun., 1683 (1970).
5. D.E. Nichols, J.M. Robinson, G.S. Li, J.M. Cassady and H.G. Floss, Org. Prep. Proced. Int., 9, 277 (1977).
6. G.S. Ponticello, J.J. Baldwin, P.K. Lumma and D.E. McClure, J. Org. Chem., 45, 4236 (1980).
7. M.p. 190-192°C (MeOH-$CHCl_3$). Fully characterised physically.
8. Characterised by physical measurements.
9. D.H.R. Barton, A.G. Brewster, R.A.H.F. Hui, D.J. Lester, S.V. Ley and T.G. Back, J.C.S., Chem. Comm., 952 (1978).

(Received in France 25 June 1985)