Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry
Publication details, including instructions for authors and subscription information:
http://www.tandfonline.com/loi/lsyc20

Chemoselective Reduction of Vinylogous Thioesters of Thiochromones

Pradeep Kumar [a] , Ashok T. Rao [a] & Bipin Pandey [a]
[a] Division of Organic Chemistry, Technology National Chemical Laboratory, Pune, 411 008, India
Published online: 23 Sep 2006.

To cite this article: Pradeep Kumar , Ashok T. Rao & Bipin Pandey (1994) Chemoselective Reduction of Vinylogous Thioesters of Thiochromones, Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry, 24:22, 3297-3306, DOI: 10.1080/00397919408010253

To link to this article: http://dx.doi.org/10.1080/00397919408010253

SYNTHETIC COMMUNICATIONS, 24(22), 3297-3306 (1994)

CHEMOSELECTIVE REDUCTION OF VINYLOGOUS THIOESTERS OF THIOCHROMONES+

Pradeep Kumar*, Ashok T. Rao and Bipin Pandey
Division of Organic Chemistry: Technology
National Chemical Laboratory, Pune - 411 008, India

Abstract: The chemoselective reduction of vinylogous thioesters of thiochromones **3** into thiochromanones **4** is described.

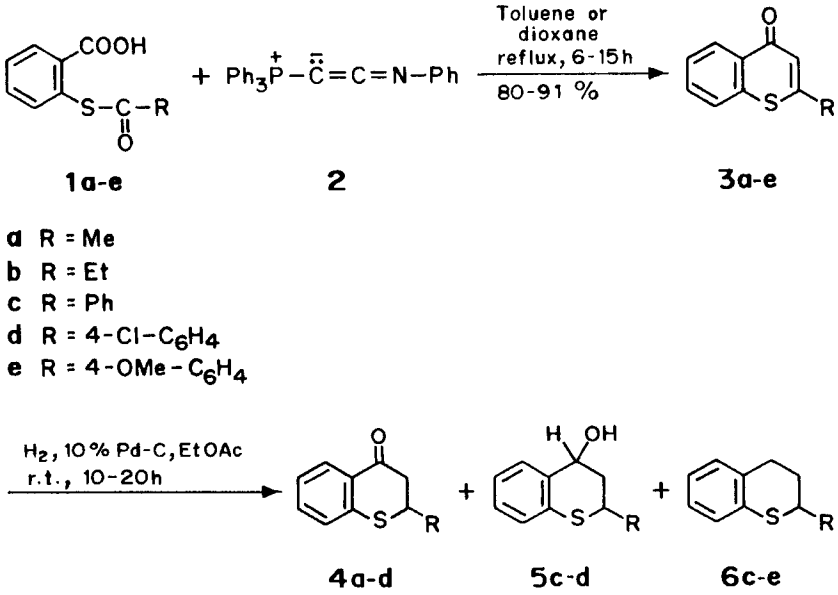
The various analogues of thiochroman-4-ones and benzothiazepins have received considerable attention due to their biological and commercial relevance.[1,2] We have recently reported an efficient methodology for thiochromones based on novel cyclization and consecutive processes involving phosphacumulene ylide as synthon.[3] In continuation, it would be interesting if reduction of 4*H*-1-benzothiopyran-4-ones (thiochromones) **3** to 2,3-dihydro-4*H*-1-benzothiopyran-4-ones (thiochromanones) **4** could be effected, which could turn out to be a valuable precursor for benzothiazepin ring system. A recent communication by Herndon et al.[4] describing the complexity of chemoselective reduction of vinylogous esters by using various reducing agents has prompted us to report our study. We were aware about

+ NCL Communication No. 5703

*To whom correspondence should be addressed.

the various methods available for the chemoselective reduction of enone to ketone e.g., hydride related reagents with/without Lewis acids and various electron transfer reagents, but we were also conscious that these methods would create problem for even remote carbon-sulfur bonds.[5-7] Perhaps this is why the majority of synthesis of these skeletons does not involve reductive methods.[8] This communication describes the results of our work on the catalytic reduction of sensitive vinylogous thioesters of thiochromones.

Scheme



The synthesis of 2-substituted thiochromones **3** could be easily accomplished by the reaction of *S*-acyl(aroyl)thiosalicylic acids **1a-e** with highly reactive *N*-phenyl(triphenylphosphoranylidene)ethenimine **2** under very mild conditions[3] (Scheme). Presumably, vinylogous thioesters should be more sensitive than vinylogous esters as C-S bonds are known to be weaker than

C-O bonds. Hence, prior to attempting any standard methods of reduction of enones to ketones, the conjugate interaction of carbon-sulfur bond to enone skeleton was visualized, which should result in an enhanced polarization of carbonyl in **3**, compared to a normal enone. Indeed the reaction of **3** with Zn/AcOH, Li/liq.NH_3, Wilkinson's catalyst, diimide[9] and cyclohexene/Pd-C 10% (catalytic hydrogen transfer)[10] failed to give the desired product. Reduction with 5% Pd-C in ethyl acetate was also not encouraging as it led to low yield of the desired products, even after prolonged reaction. Alternatively, catalytic hydrogenation of **3** with excess 10% Pd-C was attempted. A typical procedure involves hydrogenation of compound **3** (1 equiv) with 10% Pd-C (30 Wt % on the basis of substrate) at 30 psi in ethyl acetate at room temperature (Scheme). As shown in **Table**, 2-methylthiochromone **3a** on catalytic reduction using 10% Pd-C in ethyl acetate gave the desired 2-methylthiochroman-4-one **4a**. Similarly, 2-ethylthiochromone **3b** furnished the desired 2-ethylthiochroman-4-one **4b**, whereas compound **3c** under similar conditions afforded a mixture of products eg. **4c**, **5c** and **6c**. Similarly, **3d** resulted in the formation of a mixture of products **4d**, **5d** and **6d**. In contrast, **3e** under identical conditions furnished totally reduced product **6e**.[11] These results clearly indicate that the nature of substituents at 2 position in **3** influences the course of catalytic reduction. Thus, an electron-donating substituent such as *p*-methoxyphenyl at 2-position e.g., **3e** leads to complete reduction of carbonyl and secondary hydroxyl skeletons to saturated analogue **6e**, whereas an electron-attracting substituent e.g., *p*-chlorophenyl e.g., **3d** gives the ketone **4d** in addition to side products **5d** and **6d**. Besides, sulfur is known to deactivate the reactivity of Pd-C for enhancing selectivity.[6] Though

Table : Catalytic reduction of thiochromones **3** to **4**, **5** and **6**

Substrate	Reaction time/h	Product[a] Yield[b](%)	Product[a] Yield[b](%)	Product[a] Yield[b](%)
3a	10	**4a** (65)	**5a**[c] (0)	**6a**[c] (0)
3b	10	**4b** (62)	**5b**[c] (0)	**6b**[c] (0)
3c	15	**4c** (45)	**5c** (18)	**6c** (31)
3d	20	**4d** (10)	**5d** (25)	**6d** (40)
3e	15	**4e**[c] (0)	**5e**[c] (0)	**6e** (66)

a: All products were characterized by their IR, ^{1}HNMR and mass spectral data. b: The products were separated and purified by silica gel column chromatography using light petroleum-acetone 100 : 0 for **6**, 98 : 2 for **4** and 90 : 10 for **5** as eluent. c: The formation of these products could not be detected in the reaction mixture.

Pd-C catalyst (10wt % on the basis of substrate) was useful to reduce the substrate, but due to other sequential reductions, a significant amount of starting material along with varying proportion of products were recovered. Therefore, for completion of the reaction, an excess amount (30%) of the catalyst was needed. This could perhaps be attributed to the poisoning and deactivation of the catalyst due to its long exposure to the sulfur containing substrates. The side products formed during reduction are also useful skeletons.[12] Compounds **5c-d** formed during the reaction can be easily oxidized to the desired 2-substituted thiochromanones **4c-d** by known procedure.[13] Since chemoselectivity in reduction can be manipulated by the choice of a

suitable solvent,[14] the effect of various solvents was examined. However, the reduction in ethanol did not yield any product. Recently, Busacca et al.[15] have reported that dioxane can alter the chemoselectivity of reduction in related systems. However, with our substrates in dioxane, the concomitant reduction of carbonyl in **3e** could not be avoided. Alternatively, one could protect the ketone prior to catalytic reduction. However, various methods available for ketone protection[16] e.g., ethylene glycol/*p*-toluenesulfonic acid,[17] 2,2-diethyl-1,3-propanediol/pyridinium *p*-toluenesulfonate[18] also failed with these skeletons. Once again, the conjugative interaction of C-S bond might be reducing the electrophilicity of the carbonyl, ultimately creating problem for protection. It is noteworthy that analogous skeletons with varied side products have recently been reported by Clayton et al.[19] using conventional approach.

In summary, chemoselective reduction of thiochromones **3** by 10% Pd-C to thiochromanones **4** has been established. To our knowledge, this is the first report of the use of Pd-C for chemoselective reduction in these systems. The degree of chemoselectivity appears to be a function of the nature of substituent at 2-position.

EXPERIMENTAL SECTION

General Information

Melting points were determined with a Mel-Temp. apparatus and are uncorrected. Infrared spectra were recorded on a Perkin-Elmer Model 683 grating infrared spectrophotometer. Proton and ^{13}C NMR spectra were recorded on Varian FT-80A, Bruker AC-200 NMR spectrometers. The chemical shifts are reported in parts per million (δ) with tetramethyl silane as

internal standard. Mass spectra were obtained with a Finnigan MAT-1020-B-70-ev mass spectrometer.

General Method for the Catalytic Reduction of Thiochromones 3 to 4, 5 and 6

A solution of 2-substituted-4*H*-1-benzothiopyran-4-one (1 equiv.) in dry ethyl acetate was subjected to hydrogenation with 10% Pd-C (30 wt% on the basis of substrate) at 30 psi at room temp. for 10-20h (Table). The progress of reaction was monitored by TLC. The catalyst was filtered off and solvent was evaporated under reduced pressure. The crude product was purified by silica gel column chromatography using petroleum ether : acetone 100:0 for **6**, 98:2 for **4**, and 90:10 for **5** as eluent.

2-Methyl-1-benzothiopyran-4-one 3a on catalytic reduction gave **2-Methylthiochroman-4-one 4a** (65%) liquid [lit. b.p. 146-147°/9mm];[20] IR νmax/cm^{-1} (Neat) 3100-2825, 1680, 1590; ^{1}H-NMR ($CDCl_3$) δ:1.46(d, J=7.2 Hz, 3H, CH_3), 2.75-3(ddd, J=16.3, 8.8 and 2 Hz, 2H, CH_2) 3.64(m, 1H, CH), 7.16-7.4(m, 3H, Ar), 8.1 (dd, J=7.8 and 1.6 Hz, 1H, Ar); MS: *m/z*(%) M^+ 178(40), 136(100), 108(28).

2-Ethyl-1-benzothiopyran-4-one 3b on catalytic reduction gave **2-Ethylthiochroman-4-one 4b** (62%) liquid; IR νmax/cm^{-1} (Neat) 2980, 1680, 1600; ^{1}H-NMR ($CDCl_3$) δ 1.05 (t, J=7.3 Hz, 3H, CH_3), 1.4 (m, 2H, CH_2), 3.45(m, 1H, CH), 7.1-7.4(m, 3H, Ar), 8.1(dd, J=7.8 and 1.7Hz, 1H, Ar); MS: *m/z* (%) M^+ 192 (33), 166(11), 162(100), 152(40), 77(23).

2-Phenyl-1-benzothiopyran-4-one 3c on catalytic reduction gave **2-Phenylthiochroman-4-one 4c, 2-Phenylthiochroman-4-ol 5c** and **3,4-Dihydro-2-phenyl-2*H*-benzothiopyran 6c.**

4c: (45%) m.p. 50°C [lit. m.p. 51.5-52.2°][21]; IR νmax/cm^{-1} ($CHCl_3$) 2960,

1680, 1600; ^{1}H-NMR ($CDCl_3$) δ: 3.35 (q, J=7.9 and 2.6 Hz, 2H, CH_2), 4.8 (dd, J=7.9 and 2.6 Hz, 1H, CH), 7.2-7.65 (m, 8H, Ar), 8.18 (dd, J=7.9 and 1.6 Hz, 1H, Ar); MS : *m/z*(%) M^+ 240(44), 226(30), 136(100).

5c: (18%) m.p. 136-140°C [lit. m.p. 144-145°][21]; IR νmax/cm^{-1} (Nujol) 3350, 2960, 1600; ^{1}H-NMR ($CDCl_3$) δ: 2.4-2.65 (m,2H,CH_2), 4.6 (dd, J=11.6 and 3.7Hz, 1H, *CH*-C_6H_5), 5 (m, 1H, *CH*-OH), 7.15-7.9(m, 9H, Ar); MS : *m/z*(%) M^+ 242(9), 233(6), 197(22), 105(100).

6c: (31%), colourless liquid; IR νmax/cm^{-1} (Neat) 2940, 2860, 1600, 1470, 1280; ^{1}H-NMR ($CDCl_3$) δ: 2-2.2 (m, 2H, CH_2), 2.65-2.9(dd, J=5.6 and 3 Hz, 2H, Benzylic CH_2), 4.18-4.38(dd, J=6 and 3.6Hz, 1H, S-C*H*-C_6H_5), 7-7.2 (m, 9H, Ar). MS: *m/z*(%) M^+ 226(62), 135(100), 121(51), 91(60).

2-(4-Chlorophenyl)-1-benzothiopyran-4-one 3d on catalytic reduction gave **2-(4-Chlorophenyl)thiochroman-4-one 4d, 2-(4-Chlorophenyl)thiochroman-4-ol 5d** and **3,4-Dihydro-2-(4-chlorophenyl)-2*H*-benzothiopyran 6d**.

4d: (10%), colourless liquid; IR νmax/cm^{-1} (Neat) 2980, 1680, 1600, 1500; ^{1}H-NMR ($CDCl_3$) δ: 3.35 (q, J=7.3 and 2.4 Hz, 2H, CH_2), 4.75 (dd, J=12.2 and 3.9 Hz, 1H, S-*CH*-C_6H_4-Cl), 7.05-7.48(m, 7H, Ar), 8.2 (dd, J=8.3 and 2 Hz, 1H, Ar); MS: *m/z*(%) M^+ 274(5), 244(10), 226(52), 135(100).

5d: (25%) m.p. 209-210°C; IR νmax/cm^{-1} ($CHCl_3$) 3600, 2960, 1600, 1550, 1460; ^{1}H-NMR ($CDCl_3$) δ: 1.75 (br, OH), 2.38-2.65 (m, 2H, CH_2), 4.6 (dd, J=10.5 and 3.4Hz, 1H, S-*CH*-C_6H_4-Cl), 5 (q, J=12.2 and 4.9Hz, 1H, *CH*-OH), 7.2-7.9 (m, 8H, Ar); MS: *m/z*(%) M^+ 276(8), 258(5), 230(53), 138(100), 111(22).

6d: (40%), m.p. 65-69°C; IR νmax/cm^{-1} ($CHCl_3$) 2980, 1600; ^{1}H-NMR

($CDCl_3$) δ: 2.4 (m, 2H, CH_2), 3 (q, J=6.5 and 3.5 Hz, 2H, Benzylic CH_2), 4.5 (dd, J=10.9 and 3.5 Hz, 1H, S-CH-C_6H_4-Cl), 7.1 (m, 4H, Ar); 7.4 (m, 4H, Ar); MS: *m/z*(%) M^+ 260(98), 226(15), 191(18), 134(100), 120(25).

2-(4-Methoxyphenyl)-1-benzothiopyran-4-one 3e on catalytic reduction gave **6e** as only product.

6e: (66%) semisolid; IR ν/cm^{-1} ($CHCl_3$), 2980, 1600, 1480, 1400, 1280; ^{1}H-NMR ($CDCl_3$) δ: 2-2.2 (2H, m, CH_2), 2.95 (q, J=7.6 and 4.4 Hz, 2H, Benzylic CH_2), 3.75 (s, 3H, OCH_3), 4.15 to 4.35 (ddd, J=10, 4 and 1.3 Hz, 1H, S-CH-C_6H_4-OMe), 6.8-7.25(m, 9H, Ar); MS: *m/z*(%) M^+ 256(15), 226(30), 121(100).

Acknowledgement: One of us (PK) is thankful to the Department of Science and Technology, Government of India, for generous funding of the project under Young Scientist Scheme. ATR thanks the University Grants Commission, New Delhi for award of senior research fellowship. We are grateful to Dr.R.A. Mashelkar and Dr. T. Ravindranathan for support and encouragement.

References and Notes:

1 Philipp, A., Jirkovsky, I., Martel, R. R. J. Med. Chem. 1980, **23**, 1372.

2 Krapcho, J., Turk, C.F., Piala, J. J. J. Med. Chem. 1968, **11**, 361.

3 Kumar, P., Rao, A.T., Pandey, B. J. Chem. Soc., Chem. Commun. 1992, 1580.

4 Herndon, J.W., Matasi. J. J. Tetrahedron Lett. 1992, **33**, 5725.

5 For a quick survey of various methods available for reduction of enones to ketones, see: Larock, R.C. "Comprehensive Organic Transformation", VCH Publishers, Inc., New York, 1989, pp. 8-17.

6 For an exhaustive review of reductions in organic chemistry, see: Trost, B.M.,Fleming, I."Comprehensive Organic Synthesis", Pergamon Press, Plc.,England, 1991, 8.

7 For a comprehensive review of enones with varying substituents, see: Keinan, E., Greenspoon, N. in "The Chemistry of Enones", Ed. Patai, S., Rappoport, Z., John Wiley and Sons Ltd., Great Britian, 1989, Chapter 18, pp 923.

8 Tarbell, D.S., Hirschler, H.P., Hall, T.J. J. Am. Chem. Soc. 1953, **75**, 1985;Hurd, ch.D.,Hayao, S.J. Am. Chem. Soc. 1954,**76**,5065;Kunesch, G., Wessley, F. Monatsch Chem. 1965, **96**, 1547.

9 Pasto, D.J.,Taylor, R. T. Organic Reactions 1991, **40**, 91.

10 Vimal, S. D., Jain, N., Krishnamurthy, H. G. Indian J. Chem. 1994, **33B**, 163.

11 Meier, H., Schmidt, M., Eckes, H. L. Chem. Ber. 1989, **122**, 1545.

12 Hodson, H. F. Eur. Pat. 1981, 25598; Br. Pat. 1979, 318393; Goto, Y., Irukayama, Y.,Yazawa, T.,Yasuda, M.Jpn. Kokai Tokkyo Koho, 1985, 60150045; Ikegami, Y., Yagishita, A., Ishizuka, T. Jpn. Kokai Tokkyo Koho, 1985, 60222883.

13 Brown, H. C.,Garg, C. P.,Liu, K. T. J. Org. Chem. 1971, **36**, 387.

14 Augustine, R. L., Adv. Catal. 1976,**25**,56; Molnar, A. "Stereochemistry of Heterogeneous Metal Catalysis", 1985, Chapt. III, Wiley, New York.

15 Busacca, C. A.,Johnson, R. E. Tetrahedron Lett. 1992, **33**, 165.

16 Meskens, F. A. J. Synthesis 1981, 501.

17 Clemence, F., Martret, O. Le., Fournex, R., Plassard, G., Dagnaux, M. Eur. J. Med. Chem. 1974, **9**, 390.

18 DeLeeuw, J. W., De Waard, E. R., Beetz, T., Huismann, H. O. Recl. Trav. Chim. Pays-Bas 1973, **92**, 1047.

19 Clayton, S. E., Gabbutt, C. D., Hepworth, J. D., Heron, B. M. Tetrahedron 1993, **49**, 939.

20 Petropoulos, J. C., McCall, M. A., Tarbell, D. S. J. Am. Chem. Soc. 1953, **75**, 1130.

21 Hortmann, A. G., Harris, R. L., Miles, J. A. J. Am. Chem. Soc. 1974, **96**, 6119.

(Received in Japan 1 April 1994)