THE SYNTHESIS OF 2-PHENYL-3-NITRO-3,4-DIHYDRO-2H-1-BENZOPYRANS

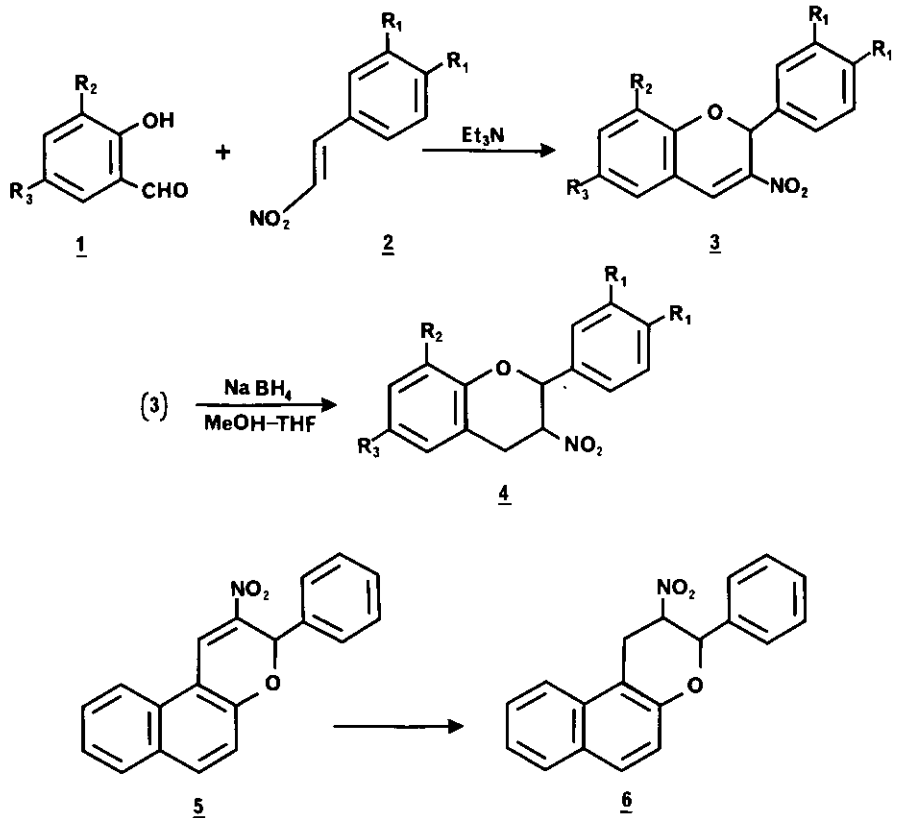
Rajender S. Varma, Miryam Kadkhodayan, and George W. Kabalka*

Department of Chemistry, University of Tennessee, Knoxville, Tennessee 37996-1600, U.S.A.

Abstract - A series of 3-nitrochromans, including a 3-phenyl-2-nitrodihydronaphtho[2,1-b]pyran, were synthesized in good yields by selective reduction of the corresponding 3-nitrochromenes using sodium borohydride in methanolic tetrahydrofuran.

Although the syntheses[1-5] and biological activity[6] of 3-nitrochromenes have attracted significant attention in recent years, the corresponding saturated analogs, the 3-nitrochromans, have virtually been ignored[7,8]. This is, in part, due to the fact that conventional techniques for the preparation of chromans from the corresponding chromenes[9,10], using catalytic hydrogenation or hydride reduction, always resulted in the formation of chromanamines[8,11,12]. Consequently, most of the nitrochromans described to date have the nitro group attached to the aromatic ring[7]; the only exception being some intermediates in the synthesis of 3-aminoflavans,[8] and a 2-methyl-3-nitrochroman[13].

Our continued interest in the chemistry of nitroalkenes[14-25] and the chemoselective reduction of α,β-unsaturated compounds[26-28] prompted us to investigate the reduction of a series of Δ^3-nitrochromenes. We found that 2-phenyl-3-nitro-2H-1-benzopyrans are readily reduced to the corresponding 2-phenyl-3-nitro-3,4-dihydro-2H-1-benzopyran at room temperature using sodium borohydride in a mixed solvent system of methanol-tetrahydrofuran (1:10, v/v). Methanol apparently reacts with sodium borohydride to form methoxyborohydride species which effectively reduce the nitrochromenes[27]. The reactions are facile and generally produce good yields of a single product. The high stereoselectivity of the reaction was confirmed by the fact that the ^{1}H nmr spectra of all of the products display only the characteristic feature ($J_{2,3}$~7 Hz) typical of trans-chromans[12,29]. In addition, only single carbon resonances were observed for the chroman ring. In the case of dihydronaphtho[2,1-b]pyran derivative, 6, however, pairs of resonances were observed in the ^{13}C-nmr spectrum of the chroman ring presumably due to a mixture of cis and trans isomers. Our results are summarized in Table I and II.



EXPERIMENTAL

Melting points were determined in capillary tubes on a Mel-Temp melting point apparatus and are uncorrected. The ^{1}H and ^{13}C nmr spectra were obtained on JEOL-FX90Q spectrometer using, unless otherwise specified, deuteriochloroform as the solvent and are referenced to TMS as the internal standard. Elemental analyses were performed by Galbraith Laboratories, Inc., Knoxville, TN.

General Procedure for the Synthesis of 2-Phenyl-Δ^{3}-nitrochromenes, 3a-f and 5.

A mixture of β-nitrostyrene (10 mmol) and o-hydroxybenzaldehyde (30 mmol) was placed in an Erlenmeyer flask and warmed on an oil bath until melted, a catalytic amount of triethylamine (1.5 mmol) was added, and the reaction mixture was left at room temperature for 20 h. The mixture was then dissolved in dichloromethane and adsorbed on basic alumina (to retain the unreacted o-hydroxybenzaldehyde). The alumina was then charged on a silica gel column. The faster moving spot, monitored by its color, was obtained in a (2-5%) ether/petroleum ether eluant and then recrystallized from methanol.

Table I

Physical and Analytical Data for Compounds 4a-f and 6

Compound No	R_1	R_2	R_3	Yield[a] [%]	M.p [°C]	Molecular Formula	Analyses (%) Calcd/Found C	H	N
4a	H	H	H	65	170-171[b]	$C_{15}H_{13}NO_3$	70.59 70.23	5.10 5.16	5.49 5.41
4b	H	OCH_3	H	82	205-206[b]	$C_{16}H_{15}NO_4$	67.37 67.37	5.26 5.44	4.91 4.76
4c	H	H	Cl	80	126[c]	$C_{15}H_{12}ClNO_3$	62.19 61.92	4.14 4.24	4.84 4.60
4d	H	H	NO_2	51	174-175[c]	$C_{15}H_{12}N_2O_5$	60.00 59.73	4.00 3.79	9.33 8.75
4e	OC_2H_5	H	H	67	143-144[b]	$C_{19}H_{21}NO_5$	66.47 66.28	6.12 6.03	4.08 3.96
4f	OC_2H_5	OCH_3	H	81[d]	147-148[b]	$C_{20}H_{23}NO_6$	64.34 63.96	6.17 5.91	3.75 3.48
6	-	-	-	85	183-184	$C_{19}H_{15}NO_3$	74.75 74.35	4.92 5.13	4.59 4.40

[a]Isolated and unoptimized yields.

[b]Recrystallization solvent: methanol.

[c]Recrystallization solvent: diethyl ether.

[d]Due to the moderate solubility of the chromene, 50 ml of solvent was used and the reaction time was 55 min.

Table II

Proton and Carbon Chemical Shifts for Compounds 4a-f[a]

Compound No	1H-NMR δ (ppm) 2H	3H	4-H	Other signals		13C-NMR δ (ppm) 2-C	3-C	4-C	Other Signals
4a	5.42 (d, $J_{2,3}$=7.9Hz, 1H)	5.13 (m, 1H)	3.47 (m, 2H)	7.74-6.9 (m, 9H, Ar-H)		78.05	84.03	29.83	-
4b	5.56 (d, $J_{2,3}$=7.0Hz, 1H)	5.05 (m, 1H)	3.42 (m, 2H)	3.85 (s, 3H, OCH_3)	7.7-6.7 (m, 8H, Ar-H)	77.97	83.74	28.86	56.08(OCH_3)
4c	5.48 (d, $J_{2,3}$=7.5Hz, 1H)	5.02 (m, 1H)	3.37 (m, 2H)	7.5-6.8 (m, 8H, Ar-H)		78.02	83.33	28.94	-
4d	5.47 (d, $J_{2,3}$= 7.2Hz, 1H)	5.02 (m, 18H, Ar-H)	3.40	7.7-6.8		78.32	82.35	27.96	-
4d	5.47 (d, $J_{2,3}$= 7.2Hz, 1H) (d, $J_{2,3}$=8.3Hz, 1H)	5.02 (m, 1 (m, 1H)	3.40 (m, 2H)	7.7-6.8 (q, 4H, 2xOCH_2) 7.4-6.7(m, 7H, Ar-H)	(t, 6H, 2xCH_3)	78.32	82.35	27.96	- 64.56(OCH_2)
4f	5.50 (d, $J_{2,3}$=6.0Hz, 1H)	5.35 (m, 1H)	3.42 (m, 2H)	4.05 (q, 2H, OCH_2) 3.78 (s, 3H, OCH_3) 7.1-6.75(m, 6H, Ar-H)	4.03 (q, 2H, OCH_2) 1.30 (t, 6H, CH_3)	78.97	84.69		15.73(CH_3) 65.89(OCH_2) 56.85(OCH_3) 65.81(OCH_2)

[a]NMR spectra were recorded in deuteriochloroform except for 4f which was obtained at 45°C in deuterioacetone.

General Procedure for the Synthesis of 2-Phenyl-2-Nitrochromanes 4a-f and 6.

The reduction of 3-phenyl-2-nitro-3H-naphtho[2,1]pyran, 5, is representative of the procedure employed. Naphtho[2,1-b]pyran, 5 (2 mmol, 0.606 g) was weighed in an Erlenmeyer flask containing a magnetic stirring bar and then 100 ml of a mixed solvent system of tetrahydrofuran-methanol (10:1, v/v) was added at room temperature. Sodium borohydride (2.5 mmol, 0.095 g) was added, in four portions, to the well stirred solution. A mildly exothermic reaction ensued with the gradual disappearance of the yellow coloration (nitrochromene). The reaction mixture was stirred for 20 min at room temperature and then quenched with water (30 ml). The volatile solvents were removed on a rotary evaporator and the aqueous suspension was extracted with dichloromethane (4 x 30 ml). The combined organic layers were wahsed with brine, dried over anhydrous magnesium sulfate, and the solvent removed under reduced pressure. Recrystallization of the crude product from ether afforded 6 (0.518 g, 85%), mp 183-184°C; ^{1}H nmr ($CDCl_3$) δ: 7.9-7.1 (m,11H,Ar-H), 5.47 (d,J=7.2 Hz, 1H, C-3H), 5.32 (m, 1H, C-2H), 3.67 (m, 2H, C-1H), ^{13}C nmr ($CDCl_3$) δ: 84.41 and 82.60 (C-2); 77.94 and 76.23 (C-3); 27.07 and 25.42 (C-1). Anal. Calcd. for $C_{19}H_{15}NO_3$; C, 74.75; H, 4.92; N, 4.59. *Found:* C, 74.35; H, 5.13; N, 4.40.

ACKNOWLEDGEMENT

We wish to thank the Department of Energy (DE-AS05-80EV10363) for the support of this research.

REFERENCES

1. R. S. Varma and G. W. Kabalka, Heterocycles, 1985, 23, 139.
2. R. S. Varma, M. Kadkhodayan and G. W. Kabalka, Synthesis (in press).
3. T. Sakakibara, M. Koezuka and R. Sudoh, Bull. Chem. Soc. Jpn., 1978, 51, 3095.
4. T. S. Rao, S. Deshpande, H. H. Mathur and G. K. Trivedi, Heterocycles, 1984, 22, 1943.
5. L. Rene and R. Royer, Eur. J. Med. Chem.-Chim. Ther., 1975, 10, 72.
6. L. Rene, L. Blanco, R. Royer, R. Cavier and J. Lemoine, Euro. J. Med. Chem.-Chim. Ther., 1977, 12, 385.
7. I. M. Lockhart, "Chromans and Tocopherols," Eds. by G. P. Ellis and I. M. Lockhart, John Wiley and Sons, Inc., New York, NY, 1981, p. 189.
8. P. K. Arora and A. P. Bhaduri, Ind. J. Chem., 1981, 20B, 951.
9. E. E. Schweizer and D. M. Nycz, "Chromenes, Chromanones and Chromenes," Eds. by G. P. Ellis, John Wiley and Sons, Inc., New York, NY, 1977, p 70.

10. E. E. Schweizer, C. J. Berninger, D. M. Crouse, R. A. Davis and R. S. Logothetis, J. Org. Chem., 1969, 34, 207.

11. G. B. Bachman and H. A. Levin, J. Am. Chem. Soc., 1948, 70, 599.

12. H. Booth, D. Huckle and I. M. Lockhart, J. Chem. Soc. Perkin Trans. II, 1973, 227.

13. I. M. Lockhart, Brit. Patent 1969, 1, 168, 228; Chem. Abstr., 1970, 72, 31618.

14. M. S. Mourad, R. S. Varma and G. W. Kabalka, J. Org. Chem., 1985, 50, 133.

15. R. S. Varma and G. W. Kabalka, Org. Prep. Proc. Int., 1985, 17, 254.

16. M. S. Mourad, R. S. Varma and G. W. Kabalka, Synth. Commun., 1984, 14, 1099.

17. M. S. Mourad, R. S. Varma and G. W. Kabalka, Synthesis, 1985, 654.

18. R. S. Varma and G. W. Kabalka, Chemistry Lett., 1984, 243.

19. R. S. Varma and G. W. Kabalka, Synth. Commun., 1985, 15, 443.

20. R. S. Varma, M. Varma and G. W. Kabalka, Tetrahedron Lett., 1985, 26, 3777.

21. R. S. Varma, M. Varma and G. W. Kabalka, Synth. Commun., 1985, 15, 1325.

22. R. S. Varma, M. Varma and G. W. Kabala, Chem. Ind. (London), 1985, 735.

23. R. S. Varma, M. Varma and G. W. Kabalka, Tetrahedron Lett., 1985, 26, 6013.

24. R. S. Varma, Y.-Z. Gai and G. W. Kabalka, Synthesis (communicated).

25. R. S. Varma, M. Varma and G. W. Kabalka, Synth. Commun., 1986, 16, 91.

26. R. S. Varma and G. W. Kabalka, Synth. Commun., 1984, 14, 1093.

27. R. S. Varma and G. W. Kabalka, Synth. Commun., 1985, 15, 151.

28. R. S. Varma and G. W. Kabalka, Synth. Commun., 1985, 15, 985.

29. J. W. Clark-Lewis, L. M. Jackman and T. M. Spotswood, Aust. J. Chem., 1964, 17, 632.

Received, 10th February, 1986