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REDUCTIVE ALKYLATION OF NITROCHROMENES. SYNTHESIS OF SPIRO-[N-HYDROXY]-LACTAMS#

S. Subramanian, Umesh R. Desai, and Girish K. Trivedi*

Department of Chemistry,
Indian Institute of Technology,
Bombay - 400 076, INDIA.

ABSTRACT: Alpha alkylation of the nitro group of nitrochromenes was performed by trapping of the nitronate salt generated by $NaBH_4$ reduction with a Michael acceptor. The adducts were used for the synthesis of spiro-[N-hydroxy]-lactams.

Nitroalkanes are amongst the strongst acids known due to the remarkable electron withdrawing ability of the nitro group. However, the yield of α-C-alkylation is good only in the case of ethane derivatives. The monoanions derived from primary and secondary nitroalkanes are prone to alkylate more at oxygen than at carbon[1]. Although many ways have

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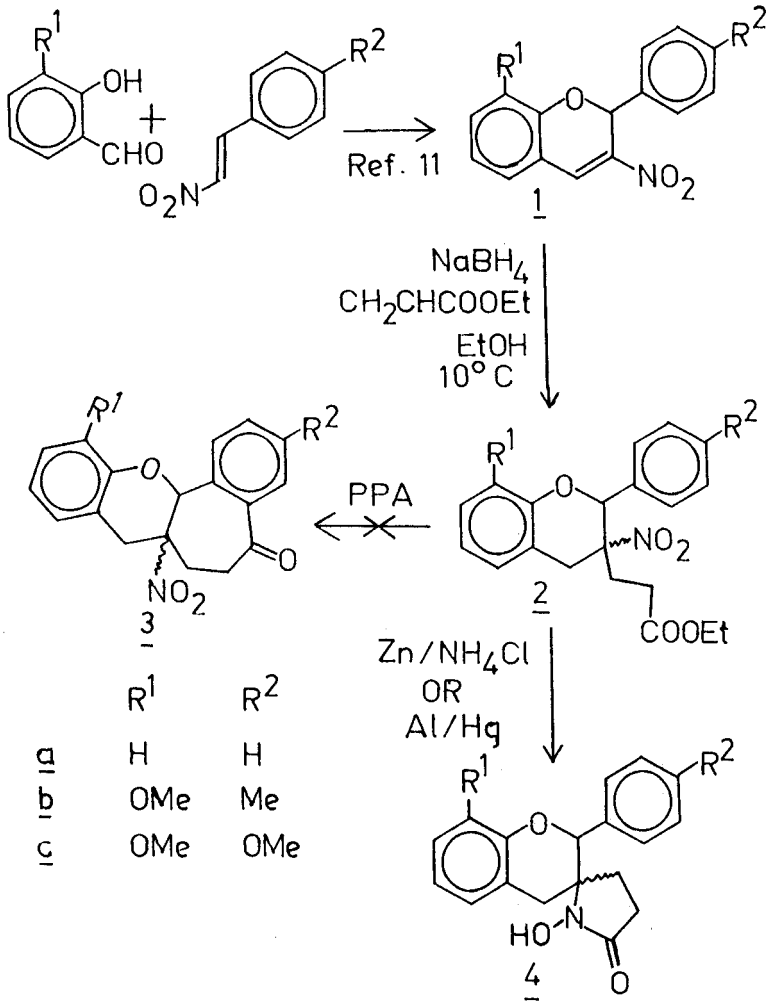
* to whom correspondence should be addressed.

Dedicated to Prof. Koji Nakanishi on the occasion of his 65th birthday.

been devised to improve C- alkylation, eg. the use of dianions[2]; preparation of solid 2-metallo-nitro derivatives[3]; use of silyl nitronates[4]; use of Al_2O_3 or Al_2O_3 coupled with KF[5]; etc.; these procedures either require expensive reagents or are technically too cumbersome to be suitable for complex substrates. We conjectured on the possibility of generating selective α-monoanions by 1,4- reduction of nitroolefins and *in situ* trapping with an electrophile like a Michael acceptor. Literature survey reveals that $NaBH_4$ reduction of β-aryl nitroolefins to β-aryl nitroethanes is a frustating job since it often leads[6-8] to poor yields of the desired products while providing more side products from the intermediate nitronate salt. An inverse addition technique has been found to give better yields[10]. Few selective reagents like lithium trialkylborohyrides are expensive for large scale preparation. Analysis of the literature data reveals that reduction with $NaBH_4$ of β-aryl nitroolefins in a 1,4-manner requires either α-methyl substitution or a strong-I inductive effect at the β-position, as exemplified by the reduction of β-(2-pyridyl)-nitroethylene[7]. Thus, we sought to alkylate the nitrochromenes 1a-c, which have the required features; i.e. -I β-inductive group and α-alkyl substitution, by trapping the α-anion with ethyl acrylate.

The nitrochromenes 1a-c were synthesized according to a procedure estabished in our laboratory[11]. When the compound 1a was exposed to $NaBH_4$ in ethanol containing excess of ethyl acrylate at 10°C, a white crystalline solid was obtained



	R^1	R^2
a	H	H
b	OMe	Me
c	OMe	OMe

Scheme I

on workup. This product had strong ir bands at 1730 cm^{-1}, and 1540 and 1380 cm^{-1}, corresponding to ester and nitro functional groups. The pmr pattern showed a multiplet at 2.42δ integrating for 4 protons indicating that reductive alkylation had indeed occurred. The elemental analysis corresponded to the expected results. Similar treatment of compounds 1b and 1c yielded the adducts 2b and 2c respectively.

We needed to prepare the fused seven membered tetracyclic compound 3 as a part of project for bioactivity screening and hence cyclisation was attempted with PPA. However, compound 2a did not yield any cyclization product owing to extensive decomposition. Hence we sought to prepare spirolactams, which required selective reduction of the nitro group in the presence of the ester group. On trying reduction with zinc-ammonium chloride on compound 2a, a colourless solid was obtained which had a molecular ion peak at 295 m/z in its mass spectrum. The ir indicated a strong hydrogen bonded group at 3160 cm^{-1}, together with a band at 1690 cm^{-1} indicative of the N-hydroxy lactam linkage. Reduction with aluminium amalgam also yielded the same compound. The other substrates 2b and 2c provided N-hydroxy lactams 4b and 4c by both methods. The reduction with aluminium amalgam appears to be better yielding.

The transformation of these N-hydroxy lactams to spiro heterocycles is currently under investigation.

EXPERIMENTAL:

All melting points are uncorrected. IR spectra were recorded on Perkin Elmer 273B spectrometer. PMR spectra were recorded on VARIAN XL100 spectrometer with TMS as internal standard. All Mass spectra were recorded on Shimadzu QP1000 spectrometer. Elemental Analyses were performed on CEST MOD .100 Instrument.

General Preparative procedure for Nitrochromene adducts 1a-c.

Nitrochromene (0.1 mol) was taken in an. Ethanol (20 mL) and left till a clear solution was obtained. Ethyl acrylate (15 g, 0.15 mol) was added and mixture cooled to 10°C. Powdered $NaBH_4$ (2.22 g, 0.06 mol) was added in small lots to the stirring solution over a period of 30 min. After further 40 min. of stirring a clear solution was obtained which was dumped into ice-water and extracted in ether. On usual work-up followed by crystallization from methanol, white needles were obtained. The analytical details are as below for each compound.

* Ethyl- 3[3'- Nitro- 2'-phenyl- benzopyran-3'-yl]-propionate 2a

Yield: 75%. mp : 61°C.

IR(KBr): $\nu(cm^{-1})$ = 1730, 1595, 1490, 1385, 1450, 1315, 1250, 1090, 1030, 930, 860, 810, 760.

^1H NMR($CDCl_3$) : δ (ppm) = 1.22(t,3H,$OCH_2\underline{CH_3}$), 2.42(m,4H,$(CH_2)_2$), 3.38(d,1H,H-4), 4.10(q,2H,$O\underline{CH_2}CH_3$), 5.44(s,1H,H-2), 7.10(m,5H,Ar), 7.44(m,4H,Ar).

Mass Fragments: (EI, m/s) = 355(M^+), 309, 91, 77.

Elemental Analysis: Calcd. C 67.60 H 5.91 N 3.94

found C 67.54 H 5.88 N 4.00

* Ethyl- 3[3'- Nitro- 2'(4''-tolyl)- 8'-methoxy-benzopyran-3'-yl]-propionate 2b

Yield: 78%. mp : 109-110°C.

IR(KBr): $\nu(cm^{-1})$ = 1735, 1600, 1545, 1500, 1470, 1380, 1340, 1095, 970, 855, 800, 790.

^1H NMR($CDCl_3$) : δ(ppm) = 1.20(t,3H,$OCH_2\underline{CH_3}$), 2.30(m,4H,$(CH_2)_2$), 2.35(s,3H,Ar-CH_3), 3.10(d,1H,H-4), 3.52(d,1H,H-4), 3.90(s,3H,OCH_3), 4.12(1,2H,$O\underline{CH_2}CH_3$), 5.48(s,1H,H-2), 7.08(m,7H,Ar).

Mass Fragments: (EI, m/z) = 399(M^+), 353, 265, 251, 162, 91, 77.

Elemental Analysis : Calcd. C 66.16 H 6.26 N 3.50

Found C 66.23 H 6.40 N 3.48.

* Ethyl- 3 [3'- Nitro- 2'(4''-Methoxyphenyl)- 9'-methoxy-benzopyran- 3'-yl]-propionate 2c

Yield : 67%. mp : 169-170°C.

IR(KBr) : $\nu(cm^{-1})$ = 1730, 1618, 1595, 1540, 1490, 1450, 1385, 1260, 1195, 970, 860, 760.

^1H NMR($CDCl_3$) : δ(ppm) = 1.19(t,3H,$OCH_2\underline{CH_3}$), 2.36(m,4H$(CH_2)_2$), 3.36(d,1H,H-4), 3.64(d,1H,H-4), 3.79(s,3H,OCH_3), 3.84(s,3H,OCH_3), 4.10(q,2H,$O\underline{CH_2}CH_3$), 5.35(s,1H,H-2), 6.90(m,3H,Ar), 7.00(d,2H,Ar), 7.32(d,2H,Ar).

Mass Fragments: (EI, m/z) = 415(M^+), 369, 91, 77.

General Procedure for Reductive Cyclization of Nitrochromene Adducts 2a-c.

Method a) Zinc Ammonium Chloride.

To a solution of nitrochromene adduct (0.001 mol) in an. Ethanol (20 mL) was added 10% NH_4Cl solution (10 mL) and heated to reflux. Zn dust (1 g) was added and solution refluxed for 2 hrs. After cooling the reaction mixture was filtered and poured into water and extracted with solvent ether. On evaporation of ether, fine crystalline material comes out.

Method b) Aluminium Amalgam.

Active aluminium amalgam was prepared by stirring fine aluminium power (500 mg) with $HgCl_2$ (500 mg) in water (25 mL) for 1 hr. and deccanting the supernatant liquid. The amalgam was washed with water and to this a solution of nitrochromene adduct (5 mmol) in a mixture of ether (10 mL) and ethanol (10 mL) is added. Stirring was continued for 24 hrs. The reaction mixture was filtered and residue washed with portions of ethanol. The filterate was evaporated to half its volume and diluted with water. This solution was extracted with ether and dried. Concentration of ether layer gives crystals of title compounds which were recrystallised from hot chloroform. The analytical details of the spiro lactams are as under.

* Spiro [3- (2-phenyl -8-methoxy- benzopyran, 5'- (N-hydroxy)-pyrrolidin- 2'-one] 4a

Yield : 52%. mp : 218°C dec.

IR(KBr) : $\nu(cm^{-1})$ = 3160, 1590, 1490, 1470, 1380, 1340, 1235, 1045, 930, 770, 710, 640.

^1H NMR($CDCl_3$) : δ(ppm) = 1.29(broad,OH), 1.90(m,4H,$(CH_2)_2$), 3.24(s,2H,H-4), 4.92(s,1H,H-2), 7.05(m,4H,Ar), 7.24(m,5H,Ar).

Mass Fragments : (EI, m/z) = 295(M^+), 278, 204, 131, 91, 77.

Elemental Analysis : Calcd. C 73.22 H 5.76 N 4.74

Found C 73.28 H 5.68 N 4.68.

* Spiro [3- (2-(4'-tolyl)- 8-methoxy- benzopyran), 5'-(N-hydroxy)- pyrrolidin- 2'-one 4b

Yield : 54% mp : 205°C chars.

IR(KBr) : $\nu(cm^{-1})$ = 1695, 1590, 1490, 1460, 1380, 1270, 1040, 960, 870, 840, 770.

^1H NMR(CD_3COCD_3) : δ(ppm) = 2.10(m,4H,$(CH_2)_2$), 2.38(s,3H,Ar-CH_3), 2.90(broad,OH), 2.92(d,1H,H-4), 3.29(s,1H,H-4), 3.78(s,3H,OCH_3), 5.00(s,1H,H-2), 6.82(m,3H,Ar), 7.25(d,2H,Ar), 7.50(d,2H,Ar).

Elemental Analysis: Calcd. C 70.79 H 6.19 N 4.13

Found C 70.91 H 6.23 N 4.20.

* Spiro [3- (2-(4'-methoxyphenyl)- 8-methoxy benzopyran), 5'- (N-hydroxy)- pyrrolidin- 2'-one]. 4c

Yield : 49%. mp : 200°C chars.

IR(KBr) : $\nu(cm^{-1})$ = 1690, 1618, 1590, 1490, 1380, 1240, 1085, 955, 840, 800, 760.

^1H NMR(CD_3COCD_3) : δ (ppm) = 2.10(m,4H,$(CH_2)_2$), 2.80(broad,OH), 2.86(d,1H,H-4), 3.28(d,1H,H-4), 3.80(s,3H,OCH_3), 3.86(s,3H,OCH_3), 5.00(s,1H,H-2), 6.82(m,3H,Ar), 6.98(d,2H,Ar), 7.56(d,2H,Ar).

Elemental Analysis: Calcd. C 67.60 H 5.91 N 3.94
Found C 67.64 H 5.87 N 4.06.

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