Synthesis of 4-substituted chromanes and 4-substituted benzo[*f*]chromanes by tandem 6-*exo-trig* cyclization-$S_{RN}1$ reactions

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Dedicated to Professor Joan Bosch on the occasion of his 60th anniversary

Abstract
4-Substituted chromanes and 4-substituted benzo[*f*]chromanes are obtained in good yields by photostimulated $S_{RN}1$ reactions of aryl halides *ortho*-substituted with butenyloxy groups with $^-SnMe_3$, $^-PPh_2$ and $^-CH_2NO_2$ ions as nucleophiles. The synthetic strategy involves the versatile application of a *6-exo trig* radical ring closure in the propagation cycle of the $S_{RN}1$ reaction. The factors governing the observed distribution of substitution products are also discussed.

Keywords: Ring-closure, 6-*exo trig*, $S_{RN}1$, dihydrochromenes, chromanes

Introduction

The unimolecular radical nucleophilic substitution reaction, or $S_{RN}1$, is a chain process that has radical and radical anions as intermediates. Since the discovery of the $S_{RN}1$ reaction in aromatic systems by Kim and Bunnett,[1] the scope of the process has increased considerably and nowadays it is accepted as a powerful tool for the formation of new carbon-carbon and carbon-heteroatom bonds. The main steps of the reaction for aromatic substrates are depicted in Scheme 1.[2]

$$ArX + e^- \xrightarrow{ET} (ArX)^{\bullet -} \quad (1)$$

$$(ArX)^{\bullet -} \longrightarrow Ar^\bullet + X^- \quad (2)$$

$$Ar^\bullet + Nu^- \longrightarrow (ArNu)^{\bullet -} \quad (3)$$

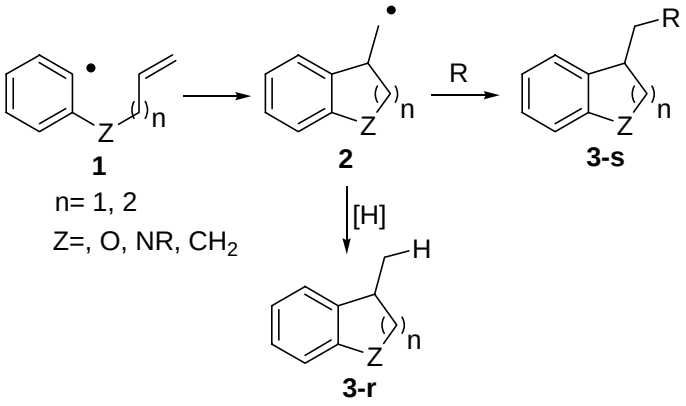
$$(ArNu)^{\bullet -} + ArX \xrightarrow{ET} ArNu + (ArX)^{\bullet -} \quad (4)$$

Scheme 1

In the initiation step (eq. 1), electron transfer (ET) from a suitable electron source forms the radical anion of the substrate, which fragments to the aryl radical $Ar^{\bullet}$ in the first step of the propagation cycle (eq. 2). The coupling of the aryl radical with the nucleophile (eq. 3) renders the radical anion of the substitution product $(ArNu)^{\bullet -}$ which propagates the chain reaction (eq. 4). Among the many means available to initiate the chain process, the photoinduced ET from nucleophiles is the usual method of choice to promote the reaction.

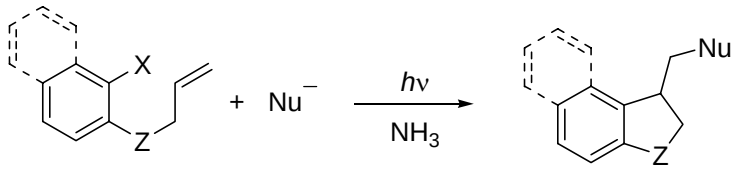
The easy access to heterocyclic compounds under very mild reaction conditions is probably the most attractive aspect of the $S_{RN}1$.[3] For example, it has been recently shown that the photostimulated reaction of carbanions of ketones with 2-iodoaniline[4] and 2-iodobenzamide[5] is an excellent method for the preparation of indoles and isoquinolinones respectively.

On the other hand, intramolecular radical addition reactions of aryl radicals to double bonds have been widely studied in regard to their regio- and stereochemical aspects.[6] Many kinetic parameters are also known.[7] Aryl halides and diazonium salts substituted in the *ortho*- position with suitable unsaturated chains have been used for the preparation of dihydrobenzofuranes, indolines, indanes and chromanes, amongst others. The general synthetic strategy involves the generation of intermediate radical **1** which rearranges to *exo*-cyclic radical **2** by 5-*exo* or 6-*exo* cyclization. Radical **2** is then trapped with a hydrogen donor to yield reduced compounds **3-r**[8] or with other reagents to obtain substituted compound **3-s**[9] (Scheme 2).



Scheme 2

Although this general scheme is a useful protocol to obtain carbo- and heterocyclic compounds, there are only few examples in which the cyclization step occurs in the propagation chain of the $S_{RN}1$ reaction. We have recently demonstrated that tandem 5-*exo* cyclization-$S_{RN}1$ reactions of aryl halides containing an *ortho*-oxyallyl and aminoallyl moieties are useful for the preparation of substituted dihydrobenzofurans, dihydronaphthofurans and indolines (eq. 5).[10]

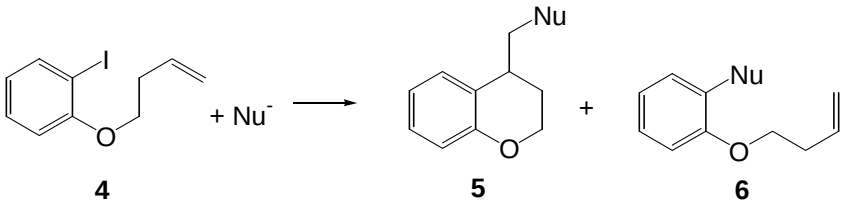


(5)

X= Cl, Br
Nu= $SnMe_3$, PPh_2, CH_2NO_2
Z= O, NCH_2CHCH_2, $NCOCH_3$

The slower 6-*exo* radical cyclization was studied to a lesser extent compared with its 5-*exo* counterpart. There are few examples of ring closure reactions taking place by intramolecular addition of an aryl radical to an *ortho*-butenyloxy pendant chain followed by a $S_{RN}1$ reaction. In most cases**,** the studies have been geared towards gathering kinetic and mechanistic information.

Beckwith[11] and Galli[12] used the *radical clock* approach to estimate the rate constant for the coupling of some nucleophiles with phenyl radicals. In the reactions of 1-but-3-enyloxy-2-iodobenzene **4** with phenylsulfide, diethylphosphite and diphenylphosphide ions, under photoinitiation in different solvents, they found mixtures of cyclized **5** and open-chain products **6** (eq. 6).



4 **5** **6**

(6)

From the relative concentration of products **5** and **6**, the rate constants for the coupling of aryl radical with the three nucleophiles were obtained ($^-SPh = 3.2\ 10^8\ M^{-1}s^{-1}$, $^-OP(OEt)_2 = 2.5\ 10^9\ M^{-1}s^{-1}$, $^-PPh_2 = 5.3\ 10^8\ M^{-1}s^{-1}$).[13]

The tandem ring-closure-$S_{RN}1$ process competes with the coupling of the nucleophile with the intermediate aryl radical. The absolute values for the rate constants of the coupling of several nucleophiles with aryl radical have been determined electrochemically and most of them are close to diffusion limit rate. Phenyl radicals are less reactive than other aryl radicals with values for rate constants for the nucleophilic attack slower than diffusion.[14]

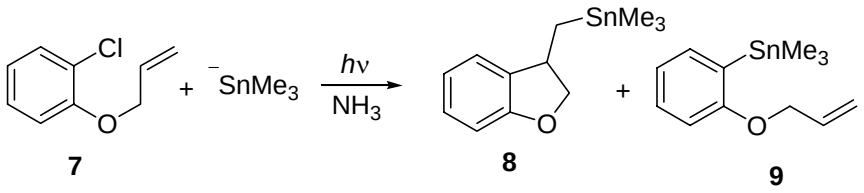
Enolate anions of ketones are probably the most studied nucleophiles in $S_{RN}1$ reactions. However, in the reactions of pinacolone and acetophenone anions with substrate **4** in DMSO, cyclized compound **5** was not formed. It has been proposed that under the reactions conditions the anions behave as bases and not as nucleophiles; the enolate takes an allylic proton promoting the elimination of 1,3-butadiene as a neutral fragment and 2-iodophenoxide ion as the leaving group.[12]

Chromenes and chromanes are widely disseminated in natural product chemistry, and it has been shown that many compounds containing this nucleus have a potent biological activity.[15,16] Antioxidant derivatives of chromenes, which are added to many foodstuffs, pharmaceuticals, and cosmetics to prevent them from becoming rancid, are the object of intensive research efforts.[17] A series of compounds with the parent chromene core structure have been synthesized and these compounds show a variety of biological activity.[18,19]

The fact that the ring-closure reaction is a unimolecular process, and therefore does not depend on the concentration of the nucleophile, in contrast to the coupling reaction, led us to believe that under dilute reaction conditions we could obtain chromanes and benzochromanes by tandem cyclisation-$S_{RN}1$ reactions using *ortho*-(3-butenyloxy)-aryl halides as starting materials. This paper describes results that successfully demonstrate this idea.

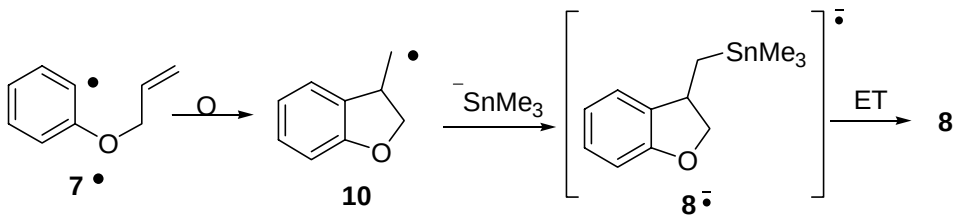
Results and Discussion

In the reaction of $^{-}SnMe_3$ ions with 1-(allyloxy)-2-chlorobenzene (**7**) in liquid ammonia under photostimulation, dihydrobenzofurane **8** was obtained as the only product in 87% yield; no substitution product **9** was detected (eq. 7).[10]



(7)

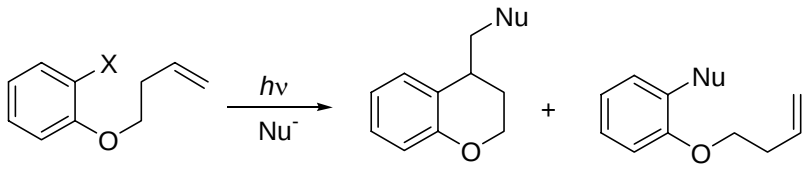
The reaction does not occur in the dark. These results indicate that an aryl radical is an intermediate and that a $S_{RN}1$ process is operating. ET to **7** gives radical **7**$^{\bullet}$ after fragmentation of the radical anion intermediate, which by a 5-*exo* cyclization forms radical **10**. The coupling of **10** with the nucleophile affords radical anion **8**$^{\bullet-}$ which by ET reaction furnishes **8** and propagates the chain reaction (eq. 8).



(8)

Under the same reactions conditions, 1-(but-3-enyloxy)-2-chlorobenzene (**11a**) reacts with $^{-}SnMe_3$ ions to afford (chroman-4-ylmethyl)trimethylstannane (**12a**) in 70% yield together

with the open-chain substitution product (**13a**) in 15% (eq. 9) (Entry 1 in Table 1). This result agrees with the expected slower ring closure rate for the 6-*exo* cyclization compared with the 5-*exo* process.



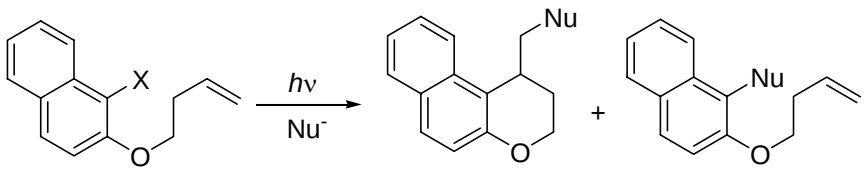
(9)

11 a; X= Cl
b; X= Br

12 a Nu = $SnMe_3$
b Nu = CH_2NO_2

13 a Nu = $SnMe_3$
b Nu = CH_2NO_2

To extend the scope of the reactions, substrate **14a** was tested in the tandem ring closure $S_{RN}1$ process with the same nucleophile (Entry 2 in Table 1). In this reaction, a high yield (91%) of cyclized compound **15a** was obtained and only traces of the by-product **16a** were formed (<3%). The expected higher reactivity of the 1-naphthyl radical, compared with that of the phenyl radical, accounts for the increased yield of cyclic compound **15a**.[20]



(10)

14 a; X= Cl
b; X= Br

15a; Nu= $SnMe_3$
b; Nu= PPh_2
c; Nu= CH_2NO_2

16a; Nu= $SnMe_3$
b; Nu= PPh_2
c; Nu= CH_2NO_2

The photostimulated reaction of $^-PPh_2$ ions with 1-(but-3-enyloxy)-2-iodobenzene in liquid ammonia, DMSO and MeCN have been previously studied.[11] A liquid ammonia solution of substrate **14a** was reacted with $^-PPh_2$ ions for 30 min. Following standard work-up, the crude reaction mixture was treated with 10% H_2O_2 solution to transform the phosphane in its more stable oxide. After recrystallization, 89% of phosphane **15b** (as its oxide) was obtained. No substitution product **16b** was detected (Entry 3 in Table 1).

Given the discouraging results obtained in the reactions of carbanions of ketones with 1-(but-3-enyloxy)-2-iodobenzene in DMSO,[12] we undertook the study of the photostimulated reactions of nitromethane anions in liquid ammonia as solvent.

It is known that the enolate anion of acetone does not react with primary alkyl radicals and that nitromethane anion does not initiate $S_{RN}1$ reactions.[21] On the other hand, acetone enolate anions can initiate $S_{RN}1$ reactions (*entrainment reagent*). The leaving group chlorine in substrates **11a** and **14a** was switched to the more reactive bromine on **11b** and **14b**.

When a liquid ammonia solution of **11b** with 4 equivalents of nitromethane anion and 2 equivalents of acetone enolate anion was irradiated for 4 h, cyclic compound **12b** was obtained in 25% yield, together with variable amounts of reduced compounds (Entry 4 in Table 1).

Using six equivalents of nucleophile and three of the *entrainment reagent*, the yield of **12b** rose to 56% (Entry 5 in Table 1), and only traces of by-product **13b** were formed (<2%). Under similar reaction conditions, substrate **14b** reacts with nitromethane anion giving cyclic nitro-compound **15c** in 76% yield (Entry 6 in Table 1). The product arising from coupling of the nucleophile in the naphthyl ring **16c** was not formed with this substrate. In these reactions, two carbon-carbon bonds were formed; the products are interesting since the nitro group can be further manipulated to obtain other useful compounds.[22]

Table 1. Tandem ring closure-$S_{RN}1$ reactions of substrates **11** and **14** with $^-SnMe_3$, $^-PPh_2$ and $^-CH_2NO_2$ ions.[a]

Entry	Substrate	Nucleophile	Products (%)[b]	% ^-X[c]
1	**11a**	$^-SnMe_3$	**12a**(70) **13a** (15)	100
2	**14a**	$^-SnMe_3$	**15a** (91) **16a** (<3)[d]	94
3[e]	**14a**	$^-PPh_2$	**15b** (89)[f]	100
4[g,h]	**11b**	$^-CH_2NO_2$	**12b** (25)[d]	33
5[h,i]	**11b**	$^-CH_2NO_2$	**12b** (56)	80
6[j,k]	**14b**	$^-CH_2NO_2$	**15c** (76)	82

[a] All reactions were performed in liquid ammonia (150 mL) as solvent using two medium pressure Hg lamps (λ max 350 nm). The irradiation time was 120 min and the concentration of the substrates was 0.0033 M and that of nucleophiles 0.0037 M.
[b] All products were quantified by GC using the internal standard method with authentic samples, unless otherwise indicated.
[c] Determined by potentiometric titration.
[d] The products were determined by ^1H NMR.
[e] The reaction time was 30 min.
[f] Isolated product yield as its oxide.
[g] The concentration of $^-CH_2NO_2$ was 0.0132 M and 0.0066 M of acetone enolate anion was used as entrainment reagent.
[h] The reaction time was 240 min.
[i] The concentration of $^-CH_2NO_2$ was 0.0198 M and of acetone enolate anion 0.0099 M.
[j] The concentration of $^-CH_2NO_2$ was 0.0198 M and of acetone enolate anion 0.0066 M.
[k] The reaction time was 180 min.

In summary, in this work we have demonstrated that the tandem ring closure-$S_{RN}1$ reaction is a useful tool for the preparation of 4-substituted chromanes and 4-substituted benzo[*f*]chromanes. When $^-CH_2NO_2$ ions are used as nucleophile, two new carbon-carbon bonds are formed in a single reaction. The pendant $SnMe_3$, PPh_2 and CH_2NO_2 groups make these products interesting since they would be easily converted into other functional groups. More work is in progress in order to extend the capability of the reaction to other heterocyclic compounds.

Experimental Section

General Procedures. The internal standard method was used for quantitative GC analysis using authentic samples, and one of the following columns was employed: HP-1 (5 m x 0.53 mm ID) or HP-1 (30 m x 0.32 mm ID column), or the products were determined by ^{1}H NMR. ^{1}H NMR (200.13 MHz) and ^{13}C NMR (50.32 MHz) were conducted in deuteriochloroform or acetone-d_6 and referenced with residual solvent signal. Coupling constants (*J*) are given in hertz. High-resolution mass spectrometric measurements were conducted at the Mass Spectrometry Facility of the University of California at Riverside. GC/MS analyses were carried out on a Shimadzu QP-5050 apparatus coupled with a mass selective detector and a DB-5 30 m x 0.25 mm ID capillary column. An Orion 420A pHmeter equipped with Ag^+/AgCl electrode was used for the potentiometric titration of the halide ions in the aqueous phases.

Materials. Chlorotrimethylstannane, triphenylphosphane, nitromethane, and *t*-BuOK were obtained from commercial sources. Acetone and nitromethane were double distilled and stored under nitrogen over molecular sieves (4 Å). Silica gel (0.063-0.200 mm) was used in column chromatography and 2 mm plates (silica gel 60 PF254) in radial thin-layer chromatography purification. All solvents were analytical grade and used as received from the supplier. Substrates **11a-b** and **14a-b** were prepared as previously indicated.[8d]

Reactions of 11a and 14a with $^-SnMe_3$ ions in liquid ammonia

Ammonia (150 mL), previously dried with Na metal, under nitrogen were condensed into a three-necked, 250 mL round-bottomed flask equipped with a coldfinger condenser charged with ethanol, a nitrogen inlet, and a magnetic stirrer. Chlorotrimethylstannane (109.6 mg, 0.55 mmol) was then added, and Na metal (30.6 mg, 1.33 mmol) in small pieces was introduced, waiting for total decoloration between each addition. A lemon yellow solution of $^-SnMe_3$ ions is obtained. The substrates were dissolved in 1 mL of dried ethyl ether and added to the solution. The reaction mixture was irradiated for 120 min using two medium-pressure mercury lamps emitting maximally at 350 nm. The reaction was quenched by adding ammonium nitrate in excess. The ammonia was allowed to evaporate, and water (50 mL) was added. The aqueous phase was extracted with dichloromethane (3 x 50 mL), and the organic phase was dried (magnesium sulfate) and the solvent evaporated in vacuum. The products were purified as indicated.

Reaction of 14a with $^-PPh_2$ ions in liquid ammonia

This reaction was performed in a fashion similar to those with $^-SnMe_3$ ions, but 0.55 mmol (144.3 mg) of PPh_3 was added instead and then Na metal (30.6 mg, 1.33 mmol) in small pieces. The addition of Na metal continued until the blue solution from solvated electrons in excess remained coloured for an additional 20 min before it became orange-brown and no more solid was present. To this solution *t*-BuOH (51 μL, 0.55 mmol) was added to neutralize the amide ions

formed. Prior to drying, the dichloromethane phase was treated with 10% H_2O_2 (50 mL) and then water (50 mL). The oxide of product **15b** was purified as indicated.

Reactions of 11b and 14b with $^-CH_2NO_2$ ions in liquid ammonia

These reactions were performed by a similar procedure to that described previously, but 3 mmol (162 μL) of nitrometane, 2 mmol acetone (147 μL) and 3.3 mmol (0.3700 g) of *t*-BuOK were added, waiting 15 min for the nucleophile and *entrainment reagent* formation.

All new compounds were characterized by standard spectroscopic techniques.

(Chroman-4-ylmethyl)-trimethyl-stannane (12a). Colourless oil purified by column chromatography using hexane-diethyl ether mixtures as solvent ^{1}H NMR ($CDCl_3$) δ: δ 7.21-7.06 (m, 2H), 6.91 (dd, ^3J = 7.4, ^4J = 1.5, 1H), 6.85-6.79 (m, 1H), 4.35-4.10 (m, 2H), 3.28-3.15 (m, 1H), 2.17-2.03 (m, 1H), 1.81-1.65 (M, 1H), 1.55-1.54 (m, 2H), 0.10 (s, $^{H\text{-}Sn}J$ = 26.5, 9H); ^{13}C NMR ($CDCl_3$) δ: 154.0, 129.0, 128.5, 127.1, 120.2, 116.7, 64.1, 32.1, 31.4, 20.0, -9.3; CG/MS (m/z): 295 (isotopic cluster, M^+ - CH_3; 58); 269 (36), 239 (15), 165 (74), 147 (94), 135 (40), 119 (26), 91 (100), 77 (40), 41 (37); EI-HRMS: calcd for $C_{13}H_{20}OSn$ (M^+ - CH_3): 297.0301. Found: 297.0305.

(2-But-3-enyloxy-phenyl)-trimethyl-stannane (13a). This compound was not isolated but detected by GC/MS and quantified assuming the same response as **12a** in FID detector of the GC. CG/MS (m/z): 295 (isotopic cluster, M^+; 60), 269 (37), 241 (42), 225 (20), 211 (27), 133 (27), 55 (100).

(Benzo[*f*]chroman-4-ylmethyl)-trimethyl-stannane (15a). Colourless oil purified by column chromatography using hexane-diethyl ether mixtures as solvent. ^{1}H NMR ($CDCl_3$) δ: 7.81-7.71 (m, 2H), 7.56 (d, ^3J = 8.8, 1H), 7.50 – 7.42 (m, 1H), 7.27 (dd, J = 15.0, ^3J = 8.0, 1H), 7.00 (d, ^3J = 8.8, 1H), 4.40 – 4.29 (m, 2H), 3.64 – 3.55 (m, 1H), 2.33 – 2.16 (m, 1H), 1.78 (qd, ^2J = 14.1, ^3J = 2.5, 1H), 1.63 – 1.06 (m, 2H), 0.16 (s, $^{H\text{-}Sn}J$ = 26.0, 9H); ^{13}C NMR ($CDCl_3$) δ: 150.7, 132.3, 129.4, 128.8, 127.7, 126.2, 122.8, 122.0, 121.0, 119.1, 61.5, 29.0, 27.7, 19.7, -9.6; CG/MS (m/z): 360 (isotopic cluster, M^+; 4), 345(79), 319 (86), 289 (23), 287 (17), 197 (64), 179 (40), 169 (43), 152 (64), 141 (66), 128 (22), 115 (55), 77 (10), 41 (30); EI-HRMS: calcd for $C_{17}H_{22}OSn$: 362.0693. Found: 362.0680.

((Benzo[*f*]chroman-4-yl)methyl)diphenylphosphane oxide (15b). White solid (mp: 189 – 190 ºC) purified by recrystallization from acetone. ^{1}H NMR ($CDCl_3$) δ: 7.95 – 7.40 (m, 12H), 7.30 – 7.22 (m, 3H), 6.98 (d, ^3J = 8.8, 1H), 4.40 – 4.28 (m, 2H), 3.92 – 3.77 (m, 1H), 2.83 – 2.46 (m, 3H), 2.26 – 2.04 (m, 1H)**;** ^{13}C NMR ($CDCl_3$) δ: 151.9, 134.7, 133.8, 132.8, 132.0, 132.0, 131.9, 131.6, 131.3, 131.1, 130.6, 130.5, 129.2, 128.9, 128.8, 128.6, 126.6, 123.0, 121.1, 119.2, 116.9, 116.6, 61.5, 34.6 (d, $^{P\text{-}C}J$ = 66), 25.8, 24.3; CG/MS (m/z); CI/NH_3 HRMS: calcd for $C_{26}H_{23}OP$ (M^+ + H): 399.1514. Found: 399.1510**.**

4-(2-Nitroethyl)-chromane (12b). Slightly yellow solid (mp: 53 – 55 ºC) purified by column chromatography using hexane-diethyl ether mixtures as solvent. ^{1}H NMR (acetone-d_6) δ: 7.25 –

7.09 (m, 2H), 6.93 – 6.76 (m, 2H), 4.73 (t, ^3J = 7.3, 2H), 4.31 – 4.13 (m, 2H), 3.00 (sext, ^3J = 5.0, 1H), 2.67 – 2.49 (m, 1H), 2.37 – 2.06 (m, 2H, overlapped), 1.99 – 1.85 (m, 1H)**;** ^{13}C NMR (acetone-d_6) δ: 155.8, 130.1, 128.7, 125.8, 121.2, 117.9, 74.4, 63.8, 34.4, 31.9, 27.3; CG/MS (m/z): 161 (M^+-NO_2, 46), 133 (23), 119 (24), 107 (47), 105 (9), 91 (21), 79 (11), 78 (20), 77 (21), 55 (100), 53 (13), 52 (12), 51 (16); EI-HRMS: calcd for $C_{11}H_{13}NO_3$: 207.0895. Found: 207.0899.

1-(But-3-enyloxy)-2-(nitromethyl)benzene (13b). Colourless oil purified by column chromatography using hexane-diethyl ether mixtures as solvent. ^{1}H NMR ($CDCl_3$) δ: 7.45 – 7.27 (m, 2H), 7.03 – 6.90 (m, 2H), 5.86 (ddt, $^3J_{trans}$ =17.2, $^3J_{cis}$ = 10.2, ^3J = 6.6,1H), 5.46 (s, 2H), 5.20 – 5.07 (m, 2H), 4.06 (t, ^3J = 6.6, 2H), 2.53 (qt, ^3J = 1.3, 6.6, 2H). ^{13}C NMR ($CDCl_3$) δ: 157.5, 134.1, 132.0, 131.6, 120.7, 118.8, 117.3, 111.7, 74.7, 67.5, 33.5. CG/MS (m/z): 207 (M^+, 17) 160 (16), 146 (28), 133 (70), 105 (100), 91 (22), 77 (46), 63 (15).

1-(2-Nitroethyl)benzo[*f*]chromane (15c). White solid (mp: 98-100ºC) purified by column chromatography using hexane-diethyl ether mixtures as solvent.^{1}H NMR (acetone-d_6) δ: 7.96 (d, ^3J =8.4, 1H), 7.80 (d, ^3J = 8.0, 1H), 7.69 (d, ^3J = 9.1 , 1H), 7.55 – 7.47 (m, 1H), 7.38 – 7.29 (m, 1H), 7.01 (d, ^3J =9.1, 1H), 5.00 – 4.74 (m, 2H), 4.37 – 4.32 (m, 2H), 3.58 –3.48 (m, 1H), 2.74 – 2.62 (m, 1H), 2.40 – 2.11 (m, 3H); ^{13}C NMR (acetone-d_6) δ: 152.7, 133.1, 130.0, 129.4, 129.2, 127.2, 123.7, 122.1, 119.7, 116.8, 73.8, 61.8, 32.1, 27.6, 24.5; CG/MS (m/z): 257 (M^+, 25), 184 (15), 183 (100), 181 (18), 165 (17), 155 (31), 153 (20), 152 (21), 115 (10), 76 (11); EI-HRMS: Anal. Calcd for $C_{15}H_{15}NO_3$: 257.1052. Found: 257.1042.

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