o-(α-Benzotriazolylalkyl)phenols: Novel Precursors of *o*-Quinone Methides

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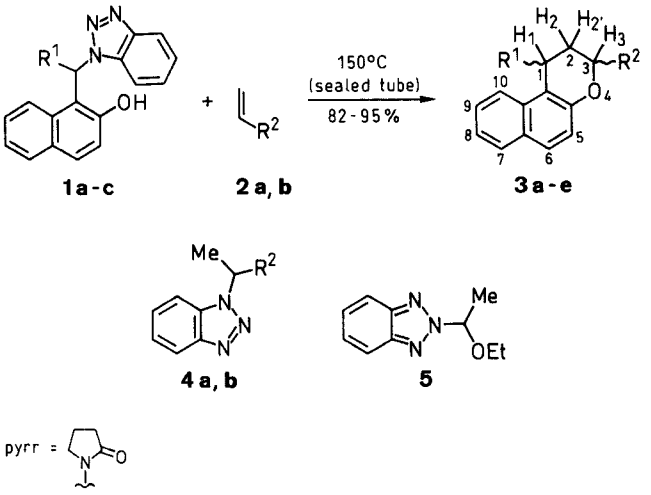
1-[α-(Benzotriazol-1-yl)alkyl]-2-napthols and 2-[(benzotriazol-1-yl)-methyl]phenols have been shown to lose a molecule of benzotriazole to generate *o*-quinone methides, which can be trapped with electron-rich olefins (ethyl vinyl ether, 1-vinyl-2-pyrrolidinone) to afford chroman derivatives, i.e. 2,3-dihydro-1*H*-naphtho[2,1-*b*]pyrans and 3,4-dihydro-2*H*-1-benzopyrans, respectively.

o-Quinone methides are reactive intermediates, useful for the construction of chroman ring systems. There are many reports concerning the use of *o*-quinone methides as heterodiene components in cycloaddition reactions with olefins.[1-3] They have been generated by thermal elimination of phenol Mannich bases,[4-6] of *o*-(α-hydroxyalkyl)benzyl alcohols,[7-9] by the oxidation of substituted *o*-alkylphenols,[10-12] and thermal or photochemical promoted cheletropic extrusion[13-15] of carbon monoxide, carbon dioxide, or sulfur dioxide. Several recent reports described generation of *o*-quinone methides from 4*H*-1,2-benzoxazines[16] and the Lewis acid catalyzed generation from *o*-[α-(alkylthio)alkyl]phenols.[17,18] The *o*-quinone methides thus generated then participate in regiospecific, intermolecular [4 + 2] cycloadditions with simple olefins, enol ethers, or enamines. Generation of *o*-quinone methides analogues by reaction of *N*-lithiated anthranilates and lithiated *ortho*-toluamides with vinylsilanes or benzynes have been reported.[19,20]

In a previous paper,[21] we reported versatile intermediates, *o*-(α-benzotriazolylalkyl)phenols, for the synthesis of substituted phenols. We suggested that some of the reactions might proceed through *o*-quinones methides as the reactive intermediates. In this report, we provide evidence for such intermediates from *o*-(α-benzotriazolylalkyl)phenols by trapping with olefins. Thus, heating an *o*-(α-benzotriazolylalkyl)phenol with an electron-rich olefin at 150 °C gave chroman derivatives in high yields.

1-[α-(Benzotriazol-1-yl)benzyl]-2-naphthol (**1a**) did not react with ten equivalents of ethyl vinyl ether (**2a**) at 120 °C, however, when the temperature was raised to 150 °C, the reaction occurred to give a diastereomeric mixture of **3a** in 92% yield. 1-(1-Ethoxyethyl)benzotriazole (**4a**) and 2-(1-ethoxyethyl)benzotriazole (**5**) were also obtained. The structures of compounds **4a** and **5** were confirmed by data comparison with those of samples previously prepared in this laboratory.[22] Compounds **4a** and **5** are presumably formed from the addition of the simultaneously generated benzotriazole to **2a**. This necessitated the use of at least two equivalents of the olefin. When only one equivalent of **2a** was used, the NMR spectra of the reaction mixture indicated the presence of starting material **1a**, along with all three products **3a**, **4a**, and **5**. Product **3a** was easily separated as a mixture of diastereomers from the byproducts **4a** and **5** by column chromatography. Compound **1a** also reacted with 1-vinyl-2-pyrrolidinone (**2b**) to give product **3b**. Starting material **2b** and compound **4b** were also observed from the NMR spectra of the crude product. The signals of **4b** were compared with those of an authentic sample prepared from the addition of benzotriazole with **2b**.[23] Trituration of the crude product with hexane/benzene gave a diastereomeric mixture of **3b** in 82% yield.



1	R^1	3	R^1	R^2
a	Ph	a	Ph	OEt
b	4-$Me_2NC_6H_4$	b	Ph	pyrr
c	H	c	4-$Me_2NC_6H_4$	OEt
2,4	R^2	d	4-$Me_2NC_6H_4$	pyrr
a	OEt	e	H	OEt
b	pyrr			

Scheme 1

Compound **1b** reacted similarly with **2a** and **2b** to afford the desired products **3c** and **3d** in high yields. In the reactions of **1b**, the presence of the byproducts **4** and **5** and other impurities made the separation of the desired products difficult because they have very close R_f values in several different solvent systems. For product **3c**, column chromatography of the crude mixture gave one fraction as the pure *cis*-isomer (*cis*-**3c**) and one fraction as the pure *trans*-isomer (*trans*-**3c**) while the other fractions were still mixtures of **3c** and **5**. For **3d**, trituration of the crude product with hexane/benzene afforded pure *cis*-**3d**; purification of the residue containing **2b**, **3d**, and **4b** by column chromatography with hexane/ethyl acetate (3:1) eliminated **2b** but still gave a mixture of **3d** and **4b**;

Table 1. Cycloaddition Products **3** and **7** from Reactions of *o*-(α-Benzotriazolylalkyl)phenols with Olefins

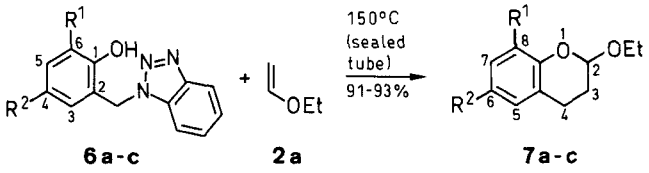
Product	Time (h)	Yield (%)[a]	mp (°C)	Molecular Formula[b] or Lit. bp (°C)/Torr	eluent (hexane/CH_2Cl_2)
3a	5	92	oil	$C_{21}H_{20}O_2$ (304.4)	5:1
3b	3	82	195–217	$C_{23}H_{21}NO_2$ (343.4)	–
3c	5	49 (92)	131–133[c]	$C_{23}H_{25}NO_2$ (347.5)	3:1
3d	3	27 (87)	243–245[c]	$C_{25}H_{26}N_2O_2$ (386.5)	3:1[d]
3e	36	95	oil	132–135/0.2[24]	2:1
7a	36	92	oil	$C_{12}H_{16}O_2$ (192.3)	4:1
7b	36	91	oil	$C_{15}H_{22}O_2$ (234.3)	6:1
7c	36	93	oil	$C_{16}H_{24}O_2$ (248.4)	5:1

[a] All yields are of pure isolated materials. For **3c** and **3d** in brackets are given the estimated total yields of the products including that obtained as mixtures, see text.
[b] Satisfactory microanalysis obtained: C ±0.4, H ±0.1, N ±0.1.
[c] Melting points of the *cis*-isomer.
[d] Hexane/EtOAc.

further attempts to purify **3d** by column chromatography were not successful. The isolated yields for **3c** and **3d** were based on the pure products obtained. The total yields for **3c** and **3d** quoted in the brackets in Table 1 were calculated from the sum of the amount of the pure products isolated and the estimated amount according to the proton integral ratios in the ^1H NMR spectra of the unseparated fractions.

With electron-deficient olefins, the reactions failed. Thus, heating **1a** and styrene at 180 °C gave starting material **1a** and some polymer. In refluxing toluene in the presence of anhydrous zinc bromide, reaction of **1a** with styrene gave a very complicated mixture and with *trans*-stilbene, it gave an uncharacterized mixture with some recovery of *trans*-stilbene.

Compounds **1c** and **6a–c**, without substituents at the position alpha to the benzotriazolyl group, are less reactive and require longer reaction times. Nevertheless, the cycloadditions of **1c** and **6a–c** with two equivalents of ethyl vinyl ether (**2a**) afforded the desired products **3e** and **7a–c** in high yields. Byproducts **4a** and **5** were also obtained in all these cases. The products were readily purified by flash column chromatography.

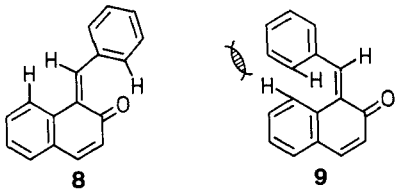


6a-c **2a** **7a-c**

6, 7	R^1	R^2
a	Me	H
b	*t*-Bu	H
c	*t*-Bu	Me

Scheme 2

The cycloaddition products, chroman derivatives **3** and **7**, were formed in a completely regiospecific manner. This can be explained in terms of the frontier orbital interactions of the LUMOs of quinone methides and the HOMOs of electron-rich olefins. Furthermore, for adducts **3a–d**, mixtures of diastereomers were obtained. The ratios of the *cis*- to the *trans*-isomers were calculated from the integral ratios of the two distinct sets of NMR signals of protons in the 1- and 3-positions, although the rest of the signals may overlap. The assignment of the signals to the specific isomer was made from the coupling constants for the protons at the 3-position with protons at the 2-position (see structure **3** in Scheme 1).[9] The *cis*-isomers, with the 1-substituents in equatorial positions, have the 3-ethoxy or pyrrolidinonyl groups in pseudoequatorial positions, while the *trans*-isomers have the 3-ethoxy or pyrrolidinonyl groups in the more stable axial positions and the 1-substituents in the equatorial positions. Thus, the coupling constants $J_{2',3}$ for the *cis*-isomers (axial-axial) are larger than those for the *trans*-isomers (equatorial-equatorial). The *trans*/*cis*-ratio for product **3a** is 2.75:1 and for product **3c** 2:1. The *trans*/*cis*-ratios for products **3b** and **3d** could not be determined because the signals of the two isomers overlapped. Our results are contrary to those reported for simple *o*-quinone methide adducts.[9] Simple *o*-quinone methides in the *E*-configuration undergo *endo*-cycloadditions with vinyl ethers to give the *cis*-isomers as the major isomers. In the cases of **1a, b** the more stable configurations for the naphtho analogs are *pseudo Z*- as shown in **8**. If an *E*-configuration is adopted, the strong H–H interaction shown in **9** prevents coplanarity of the phenyl and naphthyl rings. Thus, the *pseudo Z*-*endo*-cycloaddition affords the *trans*-isomers as the major isomers.



8 **9**

In summary, we have described novel precursors, *o*-(α-benzotriazolylalkyl)phenols, to *o*-quinone methides. The intermediates thus generated undergo cycloadditions with the electron-rich olefins ethyl vinyl ether and 1-vinyl-2-pyrrolidinone regiospecifically to give chroman derivatives in high yields. This represents the first example in which a heterocycle is eliminated in the generation of *o*-quinone methides. However, such *o*-quinone methides do not react with the electron-deficient olefins styrene and *trans*-stilbene. Furthermore, the benzotriazole generated competes with the *o*-quinone methide in reaction with the olefin, this requires the use of excess olefin and in two cases creates difficulties in the isolation of the products.

Comparison of the present method with previous routes reveals that our yields are significantly better, and the required temperature lower than for methods requiring Mannich derivatives of phenols[4,24] or *o*-(α-hydroxyalkyl)phenols.[7,9] The intermediates are easier to prepare

Table 2. ^1H NMR Data of the Cycloaddition Products **3** and **7** ($CDCl_3$/TMS) δ, J (Hz)

Product	OEt		H(1)	H(2)	H(3)	Other Aliphatic	Aromatic
	CH_3	CH_2					
cis-**3a**	1.20 (t, 3H, J = 7.1)	3.50–3.60 (m, 1H), 4.00–4.10 (m, 1H)	4.67 (dd, 1H, J = 3.6, 6.0)	2.20–2.70 (m, 4H)[a]	5.09 (dd, 1H, J = 2.4, 8.8)	–	7.00–7.20 (m, 16H), 7.35–7.45 (m, 2H), 7.65–7.75 (m, 4H)[a]
trans-**3a**	0.95 (t, 3H, J = 7.1)	3.35–3.45 (m, 1H), 3.80–3.90 (m, 1H)	4.55 (dd, 1H, J = 4.1, 7.4)		5.21 (dd, 1H, J = 2.7, 3.8)	–	
3b[b]	–	–	4.7–4.8 (m, 1H)	–[c]	5.88–5.96 (m, 1H)	2.00–2.60 (m, 6H), 3.35–3.45 (m, 1H), 3.60–3.70 (m, 1H)	7.00–7.50 (m, 9H), 7.60–7.80 (m, 2H)
cis-**3c**	1.23 (t, 3H, J = 7.1)	3.50–3.60 (m, 1H), 4.00–4.10 (m, 1H)	4.63 (dd, 1H, J = 3.7, 3.7)	2.30–2.40 (m, 2H)	5.11 (dd, 1H, J = 2.9, 8.3)	2.87 (s, 6H)	6.61 (d, 2H, J = 8.5), 6.96 (d, 2H, J = 8.5), 7.18 (d, 1H, J = 14.9), 7.20–7.30 (m, 2H), 7.45–7.55 (m, 1H), 7.65–7.75 (m, 2H)
trans-**3c**	1.02 (t, 3H, J = 7.1)	3.40–3.50 (m, 1H), 3.80–3.90 (m, 1H)	4.45 (dd, 1H, J = 4.5, 6.9)	2.20–2.40 (m, 2H)	5.16 (dd, 1H, J = 2.0, 4.4)	2.74 (s, 6H)	6.50–6.60 (m, 2H), 6.80–6.90 (m, 2H), 7.10–7.20 (m, 3H), 7.40–7.50 (m, 1H), 7.60–7.70 (m, 2H)
cis-**3d**	–	–	4.69 (dd, 1H, J = 0.9, 4.5)	–[c]	5.91 (d, 1H, J = 11.3)	2.00–2.20 (m, 3H), 2.40–2.60 (m, 3H), 2.86 (s, 6H), 3.40–3.70 (m, 2H)	6.61 (d, 2H, J = 8.1), 6.99 (d, 2H, J = 8.1), 7.10–7.30 (m, 3H), 7.50–7.80 (m, 3H)
3e	1.14 (t, 3H, J = 7.1)	3.50–3.60 (m, 1H), 3.80–3.90 (m, 1H)	2.90–3.10 (m, 2H)	1.90–2.20 (m, 2H)	5.23 (t, 1H, J = 3.5)	–	7.05 (d, 1H, J = 8.8), 7.28 (dt, 1H, J = 1.2, 8.1), 7.42 (dt, 1H, J = 1.4, 8.3), 7.57 (d, 1H, J = 8.8), 7.69 (d, 1H), 7.76 (d, 1H, J = 8.3)
7a	1.18 (t, 3H, J = 7.1)	3.60–3.70 (m, 1H), 3.80–3.90 (m, 1H)	2.50–2.60 (m, 1H), 2.90–3.00 (m, 1H)	1.80–2.00 (m, 2H)	5.26 (t, 1H, J = 3.1)	2.19 (s, 3H)	6.75 (t, 1H, J = 7.5), 6.86 (d, 1H, J = 7.4), 6.94 (d, 1H, J = 7.3)
7b	1.21 (t, 3H, J = 7.2)	3.60–3.70 (m, 1H), 3.90–4.00 (m, 1H)	2.60–2.70 (m, 1H), 2.90–3.00 (m, 1H)	1.90–2.10 (m, 2H)	5.26 (dd, 1H, J = 2.7, 4.1)	1.40 (s, 9H)	6.78 (t, 1H, J = 7.6), 6.89 (d, 1H, J = 6.8), 7.11 (d, 1H, J = 8.3)
7c	1.20 (t, 3H, J = 7.2)	3.60–3.70 (m, 1H), 3.90–4.00 (m, 1H)	2.50–2.60 (m, 1H), 2.90–3.00 (m, 1H)	1.90–2.10 (m, 2H)	5.22 (dd, 1H, J = 2.7, 4.1)	1.39 (s, 9H), 2.23 (s, 3H)	6.71 (s, 1H), 6.92 (s, 1H)

[a] The NMR spectra are reported for an inseparable mixture of diastereomers. These signals overlap.
[b] All signals overlap.
[c] The signals of H(2) overlap with signals from the pyrrolidinone ring.

than those for most of the previous routes. Also, whereas compounds **7a–c** could be prepared by previous methods, compounds **3a–d** represent a novel type. Thus, the present method should be considered as an attractive additional alternative for the generation and trapping by cycloaddition of *o*-quinone methides.

Melting points were determined using a Thomas-Hoover capillary melting point apparatus and are uncorrected. ^1H and ^{13}C NMR spectra were recorded on a Varian VXR-300 (300 MHz) spectrometer in $CDCl_3$ using TMS as an internal standard. Elemental analyses were determined at the Atlantic Microlab, Norcross, Georgia (liquids) or in this Department (solids). Compounds **1a–c** and **6a–c** were prepared by the procedure previously reported.[21]

Substituted 2,3-Dihydro-1*H*-naphtho[2,1-*b*]pyrans 3 and 3,4-Dihydro-2*H*-1-benzopyrans 7; General Procedure:

A mixture of *o*-(α-benzotriazolylalkyl)phenol **1** or **6** (1.0 mmol) and the appropriate olefin **2** (2.0 mmol) was heated at 150 °C in a sealed tube. The sealed tubes were made of thick-walled glass and used without special washing or degassing before the reactions were carried out. We observed one explosion when a simple ampoule sample tube was used for the reaction. No reactions were attempted with any solvent added. The times used for the reactions are given in Table 1. The resulting mixture was chromatographed on a silica gel column using the eluents given in Table 1.

Table 3. ^{13}C NMR Data of the Cycloaddition Proctus **3** and **7** ($CDCl_3$) δ

Product	OEt		C(1)	C(2)	C(3)	Other Aliphatic	Aromatic
	CH_3	CH_2					
cis-**3a**	15.2	64.5	37.6	36.7	96.7	–	114.2, 115.3, 118.9, 119.1, 123.11, 123.14, 123.5, 123.9, 125.6,
trans-**3a**	14.9	63.5	36.2	36.1	97.3	–	126.1, 126.3, 127.8, 128.0, 128.2, 128.3, 128.6, 128.9, 129.1, 129.4, 129.6, 132.4, 132.6, 145.5, 145.6, 150.7, 151.7[a]
3b	–	–	40.7 (38.0)[bc]	–[d]	77.5 (73.9)[c]	18.0 (17.9), 31.3 (31.4), 38.9 (33.5), 42.3 (42.2)[c]	113.3, 115.7, 118.8, 119.1, 123.0, 123.2, 123.3, 124.9, 125.7, 126.2, 126.5, 126.7, 127.0, 128.2, 128.3, 128.4, 128.7, 128.8, 129.1, 129.2, 129.3, 129.9, 132.1, 132.3, 144.4, 146.2, 152.7, 153.8, 175.6, 175.7[a]
cis-**3c**	15.3	64.7	36.83	36.81	97.1	40.5	112.7, 114.9, 118.9, 123.0, 123.6, 126.3, 128.3, 128.7, 128.9, 129.4, 132.7, 133.4, 149.0, 151.7
trans-**3c**	14.9	63.4	36.6	35.6	97.5	40.5	112.3, 116.1, 119.0, 122.9, 124.1, 125.8, 128.0, 128.5, 128.6, 129.5, 132.7, 134.0, 148.5, 150.6
cis-**3d**	–	–	37.1	–[d]	74.1	18.0, 31.4, 33.8, 40.5, 42.4	112.9, 114.1, 118.8, 123.2, 123.3, 126.4, 128.3, 128.7, 128.8, 129.3, 132.4, 132.6, 149.3, 152.5, 175.6
3e	15.1	63.7	26.3	17.3	96.7	–	114.3, 119.0, 121.9, 123.2, 126.1, 127.6, 128.3, 129.0, 132.7, 149.3
7a	15.0	63.5	26.6	20.7	96.9	15.8	119.9, 121.9, 125.8, 126.7, 128.3, 150.1
7b	15.1	64.2	26.7	21.7	97.3	29.8, 34.7	119.7, 122.6, 124.5, 127.3, 137.3, 151.0
7c	15.1	64.1	26.8	21.7	97.2	20.7, 29.8, 34.6	122.3, 125.4, 127.7, 128.5, 137.1, 148.7

[a] The signals of the two diastereomers are indistinguishable.
[b] Signals are assigned from the APT NMR spectrum.
[c] Signals appear in pairs.
[d] Signals are interchangeable with signals from the pyrrolidinone ring.

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