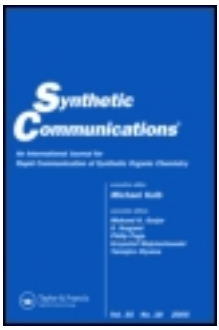

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Bromination of α-Methylstyrenes with N-Bromosuccinimide in Chlorobenzene One-Pot and Selective Preparation of 1,3-Dibromo-2-phenylprop-1-enes

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BROMINATION OF α-METHYLSTYRENES WITH *N*-BROMOSUCCINIMIDE IN CHLOROBENZENE ONE-POT AND SELECTIVE PREPARATION OF 1,3-DIBROMO-2-PHENYLPROP-1-ENES

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Abstract : A simple and selective method for the synthesis in good yield of 1,3-dibromo-2-phenylprop-1-enes **4** , the starting product to saclofen (GABA-B antagonist), is described.

γ-Aminobutyric acid (GABA), a classical inhibitory neurotransmitter, has been shown to activate at least two distinct classes of receptors subtypes, GABA-A and GABA-B receptors. GABA-B receptors are

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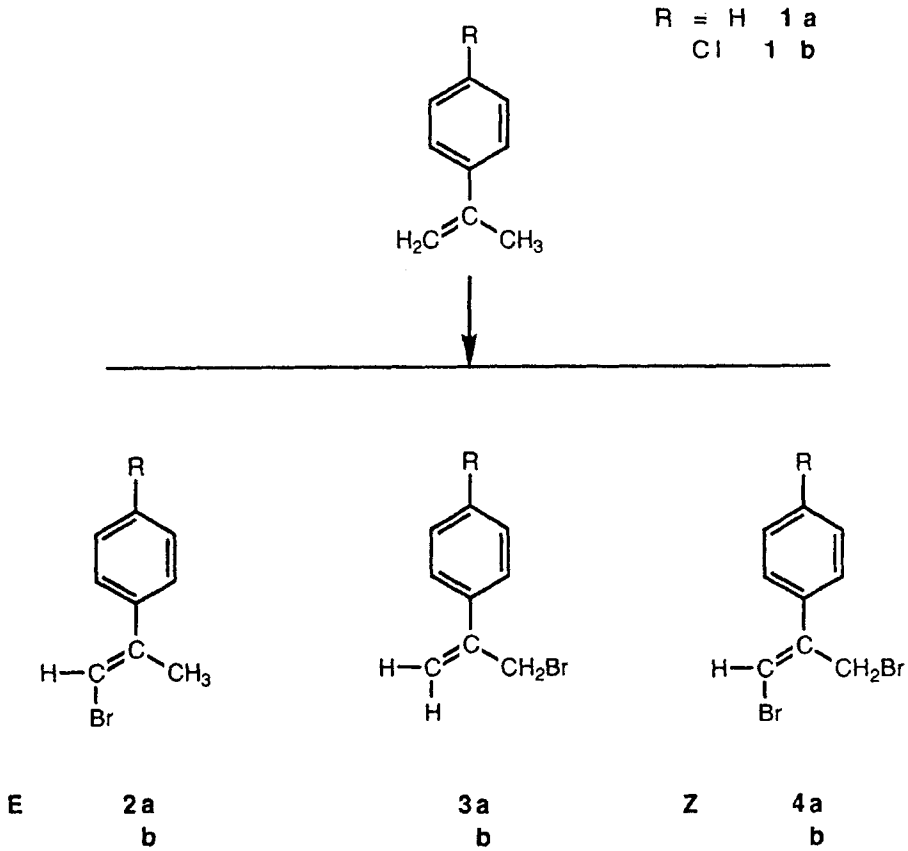
bicuculline-insensitive but are activated by baclofen (4-amino-3-(4-chlorophenyl)butyric acid) and antagonised by the phosphonic and sulphonic analogs, phaclofen (3-amino-2-(4-chlorophenyl)propylphosphonic acid), saclofen (3-amino-2-(4-chlorophenyl)propylsulphonic acid) and 2-hydroxysaclofen (3-amino-2-(4-chlorophenyl)-2-hydroxypropylsulphonic acid).[1,2]

2-Hydroxysaclofen and the most potent saclofen were described as being respectively 5 and 15 times more effective than phaclofen as GABA-B antagonists. Their synthetic pathways were published only recently[3]. In this synthesis, key step intermediates were allylic bromide **3b** and dibromide **4b** respectively. Those products were reported to be prepared from *N*-bromosuccinimide (NBS) bromination of 2-(4-chlorophenyl)propene **1b** according to a previously reported study on **1a** [4] , but no experimental details were given[3]. In the cited reference[4] only α-bromomethylstyrene **2a** and β-bromo α-methylstyrene **3a** were isolated and those in poor real overall yield (17% calculated from the starting **1a**, in large excess, and not from NBS) (see Table I) and, unfortunately, the most interesting product dibromide **4a** was not prepared. Surprisingly, the exhaustive bibliography didn't furnish more details on the synthesis and spectroscopic data of **4a-b**.[3,10]Those two aspects : i) low yield, incomplete experimental details about the synthesis of **4** and ii) our interest in the GABA-B area [5,6] in the other one prompted us to optimise this reaction in order to prepare **3** or particularly **4** rapidly and in high yield .



Scheme I

We thus carried out a more systematic study of the reaction using different solvents, reagent ratios, reaction time. In Table I are listed several conditions in which **3** or **4** can be obtained from **1** in good yield. The products were analysed in order to determine the selectivity of the reaction first using ^{1}H NMR and then preparative HPLC.

Table I. Preparation of **2**, **3**, **4** from **1** and NBS

entry	starting material	molar ratio of NBS/**1**	reaction conditions solvent	time, h	temp, °C	% yield [a] **1**	**2**	**3**	**4**
1	**1a**	0.33	CCl_4	1/4	160-170	(63)	(5)	(12)	(-) [c]
2	**1a**	0.66	CCl_4	1/4	160-170	(-)	(3)	(45)	(-) [d]
3	**1a**	1.1	C_6H_5Cl	1/4	132	0	45	55	0
4	**1a**	4.4	C_6H_5Cl	1/4	132	0	0	0	100 (58) [b]
5	**1b**	0.33	CCl_4	1/4	160-170	65	8	26	0
6	**1b**	0.66	CCl_4	1	160-170	58	32	10	0
7	**1b**	1.1	CCl_4	1/4	77	100			
8	**1b**	1.1	C_6H_5Cl	1/4	132	0	19	81 (8)	0 (35) [b]
9	**1b**	2.2	C_6H_5Cl	1/4	132	0	21	50	29
10	**1b**	2.2	C_6H_5Cl	3/4	132	0	0	0	100 (61) [b]
11	**1b**	4.4	C_6H_5Cl	1/4	132	0	20	0	80

[a] Determined by ^1H NMR of crude product
[b] Determined on purified product after preparative HPLC and calculated from the starting compound **1**
[c] Ref 4
[d] Ref 8

α-Methylstyrene **1** does not react with NBS at the temperature of boiling CCl_4 [7]. At higher temperature (160-170 °C - boiling temperature of **1**) NBS reacts to yield **3** as major product and **2** as minor product [4]. Reaction of one mole of NBS with 3 moles of **1** in CCl_4 (entries 1; 5) for 1/4 hour resulted in a mixture containing **2** and **3** in very poor yield as shown by NMR analysis. Increase in the molar ratio (entry 2) resulted in an increase of the percentage but **4** was always not observed. An excess of NBS is necessary but the boiling temperature is fixed by the solvent (CCl_4) in excess : no reaction was observed (entry 7).

So it was necessary to work at higher temperature with the possibility to dissolve an excess of NBS : we modified the procedure [4] by employing chlorobenzene. When the molar ratio NBS/**1** was 1.1 and the reaction proceeded for 1/4 hour (entries 3; 8) the starting compound **1** was completly consumed and **4** was not evidenced. The increase of the ratio and/or the increase in the time reaction lead to the best crude yield in dibromide **4** (entries 4; 10; 11). As shown in Table 1, aa average 60 % yield (after preparative HPLC) **4** can be obtained on reacting **1** with an excess of NBS in chlorobenzene at reflux for a short time.

The NMR spectra enabled us to determine the structure of all compounds(Table II). **2** showed a doublet at 2.18 (CH_3) and a quadruplet at 6.40 (CHBr) which is significative of a *E* configuration in accordance to previous data[8,9]. The coupling constants $J_{CH_3\text{-}H}$ = 1.5 confirm this structure. No *Z* isomer, which furnishes shielded signals (δ 1.97 and 6.03; $J_{CH_3\text{-}H}$ = 1.25) [9] was observed. Structure of **3** was confirmed by its chloro-analogous [8] : a singlet at 4.33 (CHBr) and a double singlet at

Table II Physical data

	^{1}H NMR in $CDCl_3$ (multiplicity, J in Hz)				R_f [b]
Compd [a]	CHBr	$=CH_2$	CH_2Br	CH_3	
1a [c]		5.03;5.34(d s)		2.09(s)	0.40
1b [c]		5.10;5.37(d s)		2.14(s)	0.45
2a	6.40(q, 1.5)			2.18(d, 1.5)	0.38
	(6.30)(q, 1.5)			(2.12)(d, 1.5) [d]	
2b	6.44(q, 1.5)			2.19(d, 1.5)	0.40
3a		5.43;5.55(d s)	4.33(s)		0.22
3b		5.45;5.55(d s)	4.33(s)		0.24
4a	6.69(s)		4.50(s)		0.26
4b	6.70(s)		4.45(s)		0.25

[a] Satisfactory analysis were obtained for all new compounds; all compounds are oils

[b] See experimental section

[c] Commercially available from Aldrich Chemical Co.

[d] Ref [9] ; CCl_4

5.44 and 5.55. For compound **4** only one isomer was also synthesized : its absolute configuration is *Z* as it was declared, but without any spectral data, in reference[3]. In fact **4** leads in the next step to the *Z* dehydrosaclofen

This selective method is of interest since it employs a quick and efficient procedure with readily obtainable starting compounds **1** giving either products **3** or particularly **4** in satisfactory yields with chlorobenzene as key solvent.

Experimental Section

^1H (80.13 MHz) NMR spectra were recorded on a Bruker WP 80 spectrometer in $CDCl_3$; tetramethylsilane was used as the internal standard of chemical shifts (δ in ppm); coupling constants (absolute values) are expressed in Hz. Deuterated solvents provided the internal lock signal. Pure samples were obtained through preparative high performance liquid chromatography (HPLC) separations performed on a Jobin-Yvon Modulprep delivery system with R.I. Iota detector, Spectro Monitor D variable wavelength detector LDC Milton-Roy (λ = 320 nm) and with a 40mm Ø column of silica gel (10-40 µm) as stationary phase and petroleum ether 40-60° as eluent. Thin layer chromatography (TLC) monitoring was performed with Merck silica gel precoated sheets (0.2 mm). The following solvent system was used: hexane/ethyl acetate 99/1; Spots were detected with ultraviolet light at λ = 254 and 366 nm.

General Procedure : Bromination of Substituted α-Methyl styrene

(See Table I for variable parameters)

The mixture styrene, NBS and solvent was rapidly heated to reflux and the reflux was maintained. The flask was quickly cooled and the solid succinimide was separated by filtration. The filtrate was evaporated to dryness under vaccuum. The relative percentages were quantified on the rough material by ^1H NMR.

In carbon tetrachloride (entry 1[4] and 5)

4-chloro α-methyl styrene (4.6 g, 0.03 mole), NBS (1.56 g, 0.009 mole) in carbon tetrachloride (1 ml)

In carbon tetrachloride (entry 7)

4-chloro α-methyl styrene (4.6 g, 0.03 mole), NBS (5.9 g, 0.033 mole) in carbon tetrachloride (10 ml)

In chlorobenzene (entry 10)

4-chloro α-methyl styrene (4.6 g, 0.03 mole), NBS (11.8 g, 0.066 mole) in chlorobenzene (10 ml). Pure analytical compound **4** was obtained through preparative chromatography : (**4b**: t_R = 79 mn; flow 10mL/mn)

Caution : the compounds prepared have lacrymatory properties ;

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