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Chemoselective *N*-Alkylation of 2-Hydroxycarbazole as a Model for the Synthesis of *N*-Substituted Pyrrole Derivatives Containing Acidic Functions

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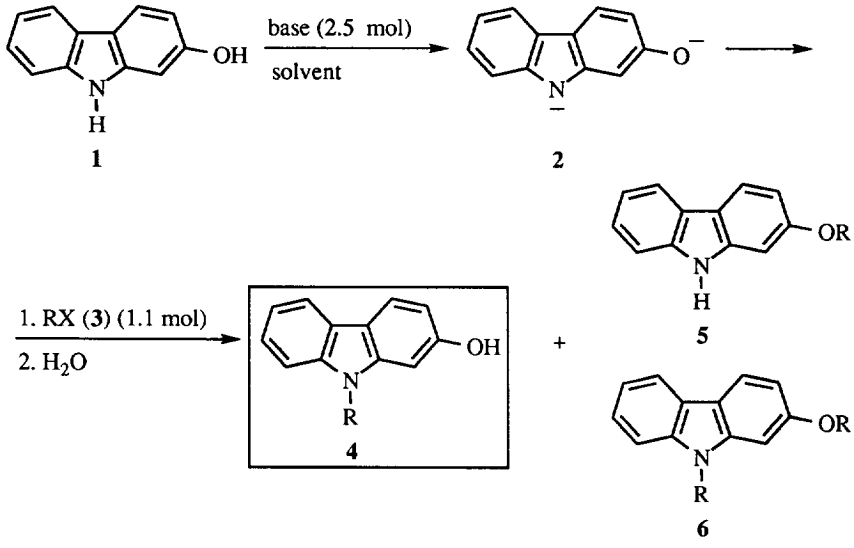
Abstract: 2-Hydroxycarbazole (1) was chemoselectively *N*-alkylated with several alkyl halides **3** by generating the corresponding *N,O*-dianion using excess sodium hydride in a suitable solvent, under anhydrous conditions. The highest yields (87-96%) of 9-alkyl-2-hydroxycarbazoles **4** and the mildest reaction conditions were reached in THF containing DMF as an additive (2 mol equiv), but other solvents (DMSO, diglyme, DME) or solvent-additive systems (THF-diglyme, THF-DMSO, DME-DMF, diglyme-DMF) are effective.

Chemoselectivity is an important problem in organic synthesis. Many chemoselective or regioselective nucleophilic substitutions are known to follow the general principle: 'whenever we desire to remove a proton at a given position for use as a nucleophile but there is a stronger acidic group in the molecule, it may be possible to take off both protons; if it is, then attack is always by the desired position since it is the ion of the weaker acid'.[1] This means that the anion derived from the weaker acid is the stronger base, but also the stronger nucleophile. Although for a set of molecules, on changing reaction conditions (e. g., solvent, temperature, etc.), basicity and nucleophilicity do not follow in all cases analogous scales, the principle cited above is, in itself, valid and has been applied in many reactions. Most are *C*-alkylations of a weaker CH-acid in the presence of a stronger (CH, NH, OH, etc.) acidic function,[2-7] but also some examples of mono-alkylations of hetero dianions have been described.[8,9]

It is known from the literature that hydroxycarbazoles[10] and the related hydroxyindoles[11] are readily *O*-mono alkylated in the presence of 1 molar equivalent of an alkylating agent RX and of a base like *n*-BuLi, NaH in an anhydrous system or NaOH, KOH, even under phase transfer catalysis (PTC) conditions. Polyalkylated products are obtained by operating with an excess of the base and of RX, in the absence of water. Whereas direct and general methods for the selective *N*-alkylation of hydroxycarbazoles and hydroxyindoles are not known, *N*-alkyl hydroxy derivatives can be prepared *via* the corresponding *O*-protected substrates, *N*-alkylation and final *O*-deprotection.[12-14]

Here we report that 2-hydroxycarbazole (**1**) is directly transformed into the 9-alkyl-2-hydroxycarbazoles

4, in a 'one-pot' reaction, by generating the corresponding *N,O*-dianion **2** with an excess of a strong base and by *N*-alkylation of **2** with alkyl halides **3** in several solvent systems and under rigorous anhydrous conditions (Scheme 1).



4-6: **a**, R = *n*-Bu; **b**, R = *n*-C_8H_{17}; **c**, R = Me; **d**, R = $PhCH_2$; **e**, R = CH_2=CH-CH_2

Scheme 1

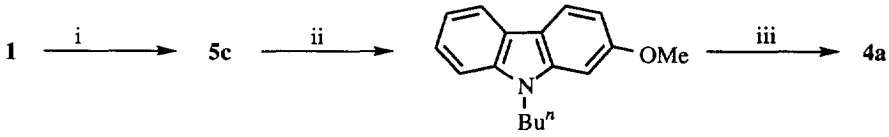
By choosing the appropriate reaction conditions (solvent, nature and amount of the base, amount of the alkylating agent, temperature) it is possible to obtain very high yields (87-96%) of **4** and to reduce the by-products of *O*-mono alkylation **5** and of *N,O*-bis alkylation **6**, thus reaching very good chemoselectivity (89-100%) on the *N*-substitution.

RESULTS AND DISCUSSION

2-Hydroxycarbazole (**1**) was deprotonated to the corresponding dianion **2** by reaction with an excess of NaH (2.5 mol equiv) as a base, in a suitable solvent, at 25 °C and under anhydrous and anaerobic conditions. The formation of **2** is complete after 10 minutes and can be qualitatively detected by the presence of a dark-green colour, whereas the *O*-monoanion is brick-red. The bis-sodium salt of **2** is only partially soluble in the medium, therefore the alkylation reactions proceed in a heterogeneous system.

The influence of the solvent on the chemoselectivity of alkylation of **2** was studied using *n*-butyl bromide (**3a**) as an alkylating agent (1.1 mol equiv), and operating at 50 °C (Table 1). The reaction in THF (entry 1) as solvent reached the maximum conversion of the substrate **1** after 22 h and 9-*n*-butyl-2-hydroxycarbazole (**4a**) was isolated in 32% yield, together with a minor amount of the *N,O*-dibutyl derivative **6a** (2%). The starting product **1** was recovered (65%) from the crude of reaction.

The identity of **4a** was confirmed by preparing it through an alternative synthetic pathway (Scheme 2). 2-Methoxy-carbazole (**5c**) was prepared by alkylation of **1** with Me_2SO_4 (**3i**) under solid-liquid (SL) PTC conditions using solid K_2CO_3 as a base, *N*-butylation of **5c** with *n*-BuBr in the presence of solid NaOH and demethylation of the resulting 9-*n*-butyl-2-methoxycarbazole (**7**) with 33% HBr/AcOH gave 9-*n*-butyl-2-hydroxycarbazole (**4a**) in 52% yield.



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i) Me_2SO_4, K_2CO_3 (solid), $TEBA_{cat}$, CH_3CN, 80 °C, 4 h. ii) *n*-BuBr, NaOH (solid), $TEBA_{cat}$, CH_3CN, 80 °C, 13 h. iii) HBr/AcOH, Δ, 4 h

Scheme 2

Interesting results were obtained by using dimethoxyethane (DME), diglyme or DMSO in lieu of THF. In particular in DMSO (entry 14) the reaction was complete in 1 h and **4a** was obtained in 82% yield, whereas in DME (entry 9) similar yields were reached after 5 h. At 50 °C diglyme was less effective (entry 11), but good yields of **4a** (82%) were obtained after 1 h by operating in this solvent at 120 °C (entry 12). Reactions carried out in DMF gave poor yields of the *N*-alkylated product **4a** and a relevant amount of the dibutylated carbazole **6a** (entry 15). An improvement in the reaction chemoselectivity and in the yield of the product **4a** was achieved by using 2 molar equivalents of a polar non-hydrogen bonding donor (non-HBD) solvent (DMF, DMSO, diglyme) as an additive, operating in a less polar solvent. The best solvent-additive system was the couple THF-DMF (Table 1, entry 3), 93% of **4a** being detected after 2 h at 50 °C, whereas at 25 °C similar conversion and yields were reached after 8 h (entry 4). By using a minor amount (1.5 mol equiv) of DMF the yields of **4a** were lowered (entry 5). The alkylation in THF-diglyme (entry 7), though in longer reaction times, gave very good yields of **4a**, whereas the systems THF-DMSO, DME-DMF and diglyme-DMF were less efficient (entries 8, 10 and 13, respectively).

The data as a whole indicate that both the reaction rate and selectivity are strongly affected by the reaction medium. In weakly non-HBD solvents, like THF (entry 1), the dianion **2** most probably exists as a high-molecular weight ion pair aggregate whose reactivity is very low.[15] The addition of a limited quantity of a more polar and good cation-solvating solvent, like DMF, DMSO and diglyme, converts ion pair aggregates of **2** into more reactive single ion pairs (entries 3, 7, 8). In these latter species the oxanion is preferentially deactivated, with respect to the azaanion, by a stronger electrostatic interaction with the alkali cation.[15] In pure DMF, DMSO and diglyme (entries 15,14,11) extensive ion pair dissociation occurs and free anions become the kinetically active species.[15] The oxanion reactivity, because there is no direct cation-anion interaction under these

conditions, approaches that of the azaanion and hence the alkylation chemoselectivity decreases (entries 11, 14, 15).

In the system THF-DMF, the use of KH instead of NaH gave poor yields of the product **4a** (entry 6), whereas the bis-lithium salt of the dianion **2**, generated using *n*-BuLi as a base in THF, was *N*-alkylated in 87% yield (entry 2). This augmented reactivity of **2** in THF is due to the higher solubility in organic media of organolithium compounds with respect to the corresponding sodium or potassium salts.

Table 1. Solvent Effect on the Chemoselectivity of *N*-Alkylation of 2-Hydroxycarbazole (**1**) with *n*-Butyl Bromide (**3a**)[a]

Entry	Solvent	Additive	t (h)[c]	Products (%)[b]			**1** (%)[b]
				4a	**5a**	**6a**	
1	THF	–	22	32	–	2	65
2	THF[d]	–	5	87	4	1	7
3	THF	DMF	2	93	1	2	2
4	THF[e]	DMF	8	91	–	3	3
5	THF	DMF[f]	27	71	1	5	21
6	THF[g]	DMF	3	28	1	10	61
7	THF	diglyme	4	94	2	3	1
8	THF	DMSO	3	86	4	8	2
9	DME	–	5	83	4	6	7
10	DME	DMF	2	86	4	9	1
11	diglyme	–	3	60	1	24	14
12	diglyme[h]	–	1	82	2	12	4
13	diglyme	DMF	1	83	2	11	4
14	DMSO	–	1	82	4	11	3
15	DMF	–	3	57	1	26	15

[a] Reaction conditions: **1** (10 mmol), solvent (20 ml), additive (20 mmol), NaH (25 mmol), **3a** (11 mmol), 50 °C.[b] HPLC yields.[c] After addition of **3a** to the preformed dianion **2**.[d] *n*-BuLi (20 mmol) instead of NaH.[e] At 25 °C[f] 15 mmol of DMF.[g] KH (25 mmol) instead of NaH.[h] At 120 °C.

To study the influence of the leaving group (X) on the alkylation of **1**, a series of *n*-octyl halides and sulphonates **3b-g** were used as alkylating agents (Table 2).

As expected the order of reactivity for the alkyl halides **3b-e** is RI > RBr > RCl >> RF (entries 1-4), e. g. with 1-iodooctane (**3b**) 2-hydroxy-9-*n*-octylcarbazole, was obtained in 91% yield after 3 h. Furthermore, the proportion of the *N*-monoalkylkated product **4a** decreases in the order I > Br > Cl > sulphonate esters (entries 1-3, 5, 6). This sequence seems to be related to the softness balance between nucleophile and leaving group.[16] A similar trend was observed in the reactions of methyl iodide (**3h**) (entry 7) and dimethylsulphate (**3i**) (entry

8). Dimethylcarbonate (**3j**) (entry 9) was found to be a selective *N*-methylating agent, but even in the presence of a large excess of **3j** low conversions were reached (50%) after longer reaction times (48 h).

Table 2. Leaving Group Effect on the *N*-Alkylation of 2-Hydroxycarbazole (**1**) [a]

Entry	RX		t (h)[c]	Products (%)[b]			
					4	**6**	**1** (%)[b]
1	*n*-$C_8H_{17}I$	(**3b**)	3	**b**	91	7	2
2	*n*-$C_8H_{17}Br$	(**3c**)	3	**b**	85	9	5
3	*n*-$C_8H_{17}Cl$	(**3d**)	19	**b**	54	11	32
4	*n*-$C_8H_{17}F$	(**3e**)	48	**b**	–	–	100
5	*n*-$C_8H_{17}OMs$	(**3f**)	1	**b**	64	19	10
6	*n*-$C_8H_{17}OTs$	(**3g**)	19	**b**	55	26	20
7	MeI[d]	(**3h**)	2	**c**	89	9	2
8	Me_2SO_4	(**3i**)	2	**c**	39	49[e]	–
9	Me_2CO_3[f]	(**3j**)	48	**c**	49	1	50

[a] Reaction conditions: **1** (10 mmol), THF (20 ml), DMF (20 mmol), NaH (25 mmol), **3** (11 mmol), 50 °C.[b] Isolated yields.[c] After addition of **3** to the preformed dianion **2**.[d] At 25 °C.[e] 11% of *O*-methyl derivative **5c** was isolated.[f] Using 22 mmol of Me_2CO_3.

Table 3. 9-Alkyl-2-hydroxycarbazoles **4a-e** Prepared by Chemoselective *N*-Alkylation of 2-Hydroxycarbazole (**1**) with Alkyl Halides, RX (**3**).[a]

RX		T (°C)	t (h)	Product	(%)[b]
n-BuBr	(**3a**)	50	2	**4a**	90
n-$C_8H_{17}I$	(**3b**)	50	3	**4b**	91
MeI	(**3h**)	25	2	**4c**	89
$PhCH_2Cl$	(**3k**)	50	5	**4d**	87
$CH_2{=}CHCH_2Cl$	(**3l**)	40	4	**4e**	96

[a] Reaction conditions: **1** (10 mmol), THF (20 ml), DMF (20 mmol), NaH (25 mmol), **3** (11 mmol).[b] Isolated yields.

Using the solvent system THF-DMF, the *N*-alkylated carbazoles **4a-e** were prepared in very good yields (Table 3), under mild reaction conditions.

In conclusion, we have shown that 9-alkyl-2-hydroxycarbazoles **4** are readily produced by chemoselective alkylation of the dianion **2**, generated from **1** in several base/solvent systems (NaH/THF-DMF, NaH/DMSO, NaH/diglyme or *n*-BuLi/THF).

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EXPERIMENTAL

All the solvents for preparative reactions were purchased as anhydrous reagents (Fluka) and used as such. THF used in the reactions analysed by HPLC was distilled over $LiAlH_4$. 2-Hydroxycarbazole (**1**) was recrystallised from water/EtOH (20:80) and desiccated under vacuum (0.1 Torr), at 50 °C and in the presence of P_2O_5 for 24 h. Commercial alkylating agents **3a-e,h-l** were distilled under Ar and stored over molecular sieves (0.4 nm) before use. *n*-Octyl methanesulphonate[17] (**3f**) and *p*-toluenesulphonate[18] (**3g**) are known compounds and were prepared from *n*-octan-1-ol through standard procedures. HPLC analyses were performed on Hypersil BDS C18 5μm (250 x 4.6 mm) (Shandon) or μ-Bondapak C18 10μm (300 x 3.9 mm) (Waters) columns, using MeOH : H_2O (80 : 20)/MeOH with a variable gradient as a mobile phase and UV detection (λ = 286 nm). ^1H NMR spectra were recorded in $CDCl_3$ at 80, 200 or 300 MHz, using TMS as external standard; the values of coupling constants are in Hz. FT-IR spectra were recorded as Nujol mull. Melting points are corrected.

General Method for the Chemoselective Preparation of 9-Alkyl-2-hydroxycarbazoles **4**

In a well dried apparatus (two-necked round bottomed flask with a condenser, a silicon septum and magnetic stirring), under Ar atmosphere , 80% NaH (0. 75 g, 25 mmol) is rinsed three times with 2 ml of anhydrous *n*-pentane and finally dried under Ar flow. To the base are added by syringe (10 minutes) 20 ml of a solution of **1** (1.83 g, 10 mmol, 0.5 M) and of DMF (1.47 ml, 20 mmol, 1.0 M) in THF, under stirring, at room temperature. After evolution of hydrogen (10 min), the alkylating agent **3** (11 mmol) is added by syringe to the dianion **2** and the stirring is continued at 25-50 °C until maximum conversion of the substrate (TLC and HPLC) is reached. After this time the reaction mixture is cooled to 0 °C and quenched with water (5 ml), the solvent is evaporated under vacuum and the crude of the reaction purified on silica gel (230-400 mesh) by medium pressure liquid chromatography (MPLC). Alkylating agent, temperature and reaction time, MPLC eluant, yield and physical, spectroscopic, and analytical data of the products **4-6** are as follows.

9-n-Butyl-2- hydroxycarbazole (4a). *n*-BuBr (**3a**), 50 °C, 2 h; Et_2O and petroleum ether (PE) (1 : 4); **4a**, 90%; mp 128.6 °C; ^1H NMR (200 MHz), δ, 8.01 (d, 1 H, *J* = 7.8), 7.93 (d, 1 H, *J* = 8.3), 7.42-7.15 (m, 3 H), 6.83 (d, 1 H, *J* = 2.1), 6.71 (dd, 1 H, *J* = 2.1, 8.4), 4.98 (bs, 1 H), 4.20 (t, 2 H, *J* = 7.2), 1.90-1.76 (m, 2 H), 1.55-1.31 (m, 2 H), 0.94 (t, 3 H, *J* = 7.3); IR (ν_{OH}) 3209 cm^{-1}. *Anal. Calcd.* for $C_{16}H_{17}NO$: C, 80.29; H, 7.17; N, 5.85. *Found*: C, 80.40; H, 7.12; N, 5.79. 2-*n*-Butyloxycarbazole (**5a**), 1%; mp 211-212 °C; ^1H NMR (80 MHz), δ, 8.03-7.84 (m, 2 H), 7.43-7.07 (m, 3 H), 6.91-6.75 (m, 2 H), 6.71 (s, 1 H), 4.04 (t, 2 H, *J* = 6.4), 2.04-1.31 (m, 4 H), 1.00 (t, 3 H, *J* = 7.1); IR (ν_{NH}) 3389 cm^{-1}. *Anal. Calcd.* for $C_{16}H_{17}NO$: C, 80.29; H, 7.17; N, 5.85. *Found*: C, 80.46; H, 7.25; N, 5.65. 9-*n*-Butyl-2-*n*-butyloxycarbazole (**6a**); 2%; mp 71 °C; ^1H NMR (200 MHz), δ, 7.95 (t, 2 H, *J* = 8.1), 7.42-7.15 (m, 3 H), 6.86-6.81 (m, 2 H), 4.24 (t, 2 H, *J*

= 7.2), 4.10 (t, 2 H, *J* = 7.2), 1.92-1.78 (m, 4 H), 1.65-1.32 (m, 4 H), 1.02 (t, 3 H, *J* = 7.3), 0.95 (t, 3 H, *J* = 7.3). *Anal. Calcd.* for $C_{20}H_{25}NO$: C, 81.30; H, 8.55; N, 4.74. *Found*: C, 81.02; H, 8.36; N, 4.70.

9-n-Octyl-2-hydroxycarbazole (4b). *n*-$C_8H_{17}I$ (**3b**), 50 °C, 3 h; Et_2O and PE (1 : 4); **4b**, 91%; mp 86-88 °C; ^1H NMR (80 MHz), δ, 7.96-7.76 (m, 2 H), 7.35-7.00 (m, 3 H), 6.78-6.68 (m, 1 H), 6.56 (d, 1 H, *J* = 2.1), 5.01 (bs, 1 H), 4.12 (t, 2 H, *J* = 7.1), 2.00-0.59 (m, 15 H); IR (ν_{OH}) 3323 cm^{-1}. *Anal. Calcd.* for $C_{20}H_{25}NO$: C, 81.30; H, 8.55; N, 4.74. *Found*: C, 81.26; H, 8.47; N, 4.65. 9-*n*-Octyl-2-*n*-octyloxycarbazole (**6b**), 7%; n_D^{20} 1.5580; ^1H NMR (80 MHz), δ, 8.21-7.82 (m, 2 H), 7.51-7.01 (m, 3 H), 6.93-6.84 (m, 1 H), 6.78 (d, 1 H, *J* = 2.3), 4.21 (t, 2 H, *J* = 7.0), 4.07 (t, 2 H, *J* = 7.0), 2.06-0.58 (m, 30 H). *Anal. Calcd.* for $C_{28}H_{41}NO$: C, 82.48; H, 10.16; N, 3.44. *Found*: C, 82.60; H, 10.23; N, 3.36.

9-Methyl-2-hydroxycarbazole (4c). MeI (**3h**), 25 °C, 2 h; Et_2O and PE (1 : 1.5); **4c**, 89%; mp 166-167 °C (lit.[19] 166-168 °C); ^1H NMR (80 MHz), δ, 8.00 (d, 1 H, *J* = 7.9), 7.93 (d, 1 H, *J* = 8.3), 7.47-7.19 (m, 3 H), 6.84-6.72 (m, 2 H), 4.99 (s, 1 H), 3.78 (s, 3 H); IR (ν_{OH}) 3268 cm^{-1}. 9-Methyl-2-methoxycarbazole (**6c**), 9%; mp 102 °C (lit.[20]99-100 °C); ^1H NMR (300 MHz), δ, 8.01 (d, 1 H, *J* =7.7), 7.97 (d, 1 H, *J* = 9.1), 7.44-6.84 (m, 3 H), 6.89 (d, 1 H, *J* = 2.3), 6.85 (dd, 1 H, *J* = 2.3, 3.6), 3.95 (s, 3 H), 3.79 (s, 3 H).

9-Benzyl-2-hydroxycarbazole (4d). $PhCH_2Cl$ (**3k**), 50 °C, 5 h; Et_2O and PE (1.5 : 1); **4d**, 87%; mp 185-186 °C; ^1H NMR (200 MHz), δ, 8.04 (d, 1 H, *J* = 5.2), 7.96 (d, 1 H, *J* = 5.3), 7.41-7.14 (m, 8 H), 6.78 (s, 1 H), 6.75 (d, 1 H, *J* = 1.4), 5.43 (s, 2 H), 4.98 (bs, 1 H); IR (ν_{OH}) 3338 cm^{-1}. *Anal. Calcd.* for $C_{19}H_{15}NO$: C, 83.48; H, 5.54; N, 5.13. *Found*: C, 83.40; H, 5.54; N, 5.13. 9-Benzyl-2-benzyloxycarbazole (**6d**), 5%; mp 171-173 °C; ^1H NMR (300 MHz), δ, 8.03 (t, 2 H, *J* = 5.8), 7.49-7.14 (m, 13 H), 6.98-6.93 (m, 2 H), 5.46 (s, 2 H), 5.14 (s, 2 H). *Anal. Calcd.* for $C_{26}H_{21}NO$: C, 85.91; H, 5.84; N, 3.85. *Found*: C, 85.78; H, 5.80; N, 3.93.

9-Allyl-2-hydroxycarbazole (4e). 3-Chloroprop-1-ene (**3l**), 40 °C, 4 h; Et_2O and PE (1.5 : 1); **4e**, 96%; mp 119 °C; ^1H NMR (300 MHz), δ, 7.99 (d, 1 H, *J* = 7.5), 7.91 (d, 1 H, *J* = 5.3), 7.41-7.19 (m, 3 H), 6.80 (d, 1 H, *J* = 2.1), 6.75 (dd, 1 H, *J* = 2.4, 8.7), 6.01-5.88 (m, 1 H), 5.65 (bs, 1H), 5.14 (dd, 1 H, *J* = 1.2, 10.3), 5.03 (dd, 1 H, *J* = 1.2, 17.1), 4.79-4.77 (m, 2 H); IR (ν_{OH}) 3352 cm^{-1}. *Anal. Calcd.* for $C_{15}H_{13}NO$: C, 80.68; H, 5.88; N, 6.27. *Found*: C, 81.03; H, 5.71; N, 6.39.

Synthesis of 2-Alkyloxycarbazoles (5) Under Solid-Liquid PTC Conditions

Representative preparation. A heterogeneous mixture of an organic solution of **1** (366 mg, 2 mmol), triethylbenzylammonium chloride (TEBA) (46 mg, 0.2 mmol) and *n*-BuBr (**3a**) (215 μl, 2 mmol) in CH_3CN (6 ml) and anhydrous K_2CO_3 (553 mg, 4 mmol) is stirred at 80 °C for 4 h. After this time the crude is cooled, filtered on Celite and the solvent evaporated under vacuum. The residual is chromatographed (MPLC) using Et_2O : PE (1 : 4). The *O*-monobutyl derivative **5a** is isolated in 81% yield, mp 211 °C; its ^1H NMR and IR spectra are identical to those registered from **5a** obtained as by-product in the synthesis of **4a**.

In a similar way, by using Me_2SO_4 (**3i**) (199 μl, 2.1 mmol) as alkylating agent, 2-methoxycarbazole (**5c**) is prepared in 85% yield, mp 233 °C (lit.[20] 232-233 °C); ^1H NMR (300 MHz), δ, 8.00 (bs, 1 H), 7.97 (d, 1 H,

J = 7.8), 7.93 (d, 1 H, J = 8.4), 7.39-7.18 (m, 3 H), 6.91 (d, 1 H, J = 2.1), 6.85 (dd, 1 H, J = 2.1, 8.7), 3.90 (s, 3 H); IR (ν_{NH}) 3389 cm^{-1}.

*Synthesis of (**4a**) by O-demethylation of 9-n-Butyl-2-methoxycarbazole (7)*

A heterogeneous mixture of an organic solution of 2-methoxycarbazole (**5c**) (197 mg, 1 mmol), triethylbenzylammonium chloride (TEBA) (23 mg, 0.1 mmol), and *n*-BuBr (**3a**) (108 µl, 1 mmol) in CH_3CN (5 ml) and solid NaOH (80 mg, 2 mmol) is stirred at 80 °C for 13 h. After usual work up the residual is analysed by ^1H NMR and shows signals at δ, 4.25 (t, 2 H, J = 7.2), 3.98 (s, 3 H). This crude is diluted with 1.5 ml of 33% HBr in AcOH and refluxed for 4 h. After cooling, the solvent is stripped under vacuum, the residual is diluted with CH_2Cl_2 (10 ml) and washed three times with a 5% $NaHCO_3$ solution and water, respectively, dried over $MgSO_4$, stripped and chromatographed using Et_2O : PE (1 : 2). The product **4a** is obtained in 52% yield, mp 128.5 °C; its spectroscopic data are identical to those of compound **5a** isolated from the chemoselective alkylation of **1**.

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