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Arylcarbinols as nerve agent probes. Influence of the conjugation in the sensing properties

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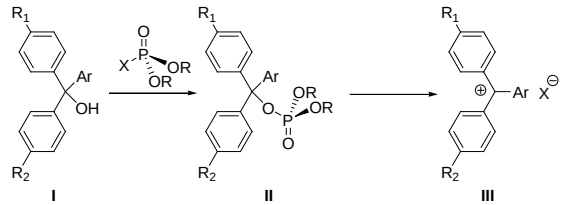
Two new aryl carbinols (1 and 3) have been synthesised and characterised and their ability as OFF-ON probes for the chromogenic detection of the nerve agent simulant in acetonitrile has been tested. In addition compound 2 has been also studied. The carbinols suffered a phosphorylation reaction followed by an elimination process giving rise to the corresponding carbocations. This transformation of the carbinol into the carbocation is responsible for a significant color change.

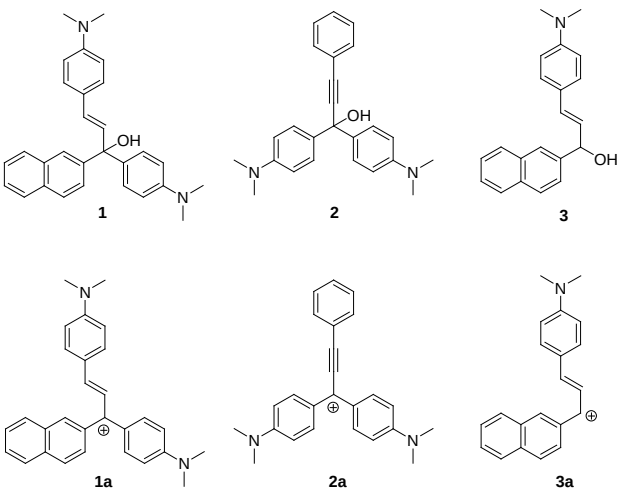
Introduction

The current increase in international concern in relation to criminal terrorism has brought about rising interest in the development of reliable detection techniques of chemical warfare (CW) agents. Among them, nerve agents are especially dangerous species and poisoning may occur through inhalation or consumption of contaminated liquids or foods.[1] Chemically, nerve gases are highly toxic phosphoric acid esters, structurally related to the larger family of organophosphate compounds. The extreme toxicity of these compounds is due to their ability to bind primarily and rapidly to acetylcholinesterase (AChE) in the neuromuscular junction of the central nervous system.[2] These organophosphates also have the ability to bind butyrylcholinesterase (BChE) in blood. The high vapour pressures of these nerve agents and their rapid effect on the central nervous system, combined with the low cost and unsophisticated technology required for production, make these compounds among the preferred choices for terrorists. For this reason, tools which combine reliability and rapidity of response for the detection of these lethal chemicals are strongly required. Thus, in addition to the detection systems based on enzymatic and physical methodologies[3] the development of fluorogenic chemosensors or reagents, as an alternative to these classical methods, has gained interest recently.[4] During the last years we have been involved in the design and synthesis of chromo-fluorogenic chemosensors for the detection of nerve agents.[5]



Scheme 1 Mechanism of the chromogenic response of carbinols **1-3** in the presence of warfare agent simulants.

During this research we have recently demonstrated that triarylcarbinols are suitable systems for detecting these reactive compounds.[6] Triarylcarbinols can be converted into their corresponding carbocations being this reaction directly related to strong colour changes.[7] The known reactivity of phosphate and phosphonate with hydroxyl groups, makes it possible the sensing mechanism. The sensing protocol is shown in Scheme 1; the hydroxyl group present in the carbinol (**I**) is able to experiment phosphorylation reactions with phosphonate substrates to form the intermediate **II** which experiments easily an elimination reaction giving rise to the corresponding carbocation **(III)**. Transformation of **I** in **III** is concomitant with the formation of a highly delocalised system that is responsible for a significant colour modulation.



Scheme 2 Chemical structure of carbinols **1-3** and its correspondent carbocations **1a-3a**

Based in this protocol, we report herein the synthesis and characterization of three new carbinols (**1**-**3**) and their use as probes for the detection of nerve agents simulants (see Scheme 2).

Experimental

General procedures and materials. All reagents commercially available were used without purification. Silica gel 60 F254 (Merck) plates were used for TLC. ^{1}H and ^{13}C NMR spectra were recorded with the deuterated solvent as the lock and residual solvent as the internal reference. High-resolution mass spectra were recorded in the positive ion mode on a VG-AutoSpec. UV-vis spectra were recorded using a 1 cm path length quartz cuvette.

Synthesis of *p*-dimethylaminonaphthylideneketone (**4**). 4-Dimethylaminobenzaldehyde (97%, 1.044 g, 6.79 mmol) and 2-acetylnaphthalene (1.160 g, 6.79 mmol) were dissolved in EtOH (10 mL). Then NaOH (2 mL, 40% in water-EtOH (4:1)) was added to the mixture and then it was stirred overnight at room temperature. The reaction was poured over water (100 mL) to get an orange solid. The solid was dried in the oven at 60 ºC and recrystallized from MeOH to obtain **4** (1.2 g, 59%) as an orange solid. ^{1}H NMR (300 MHz, d_6-acetone) δ 8.66 (d, *J* = 0.7 Hz, 1H), 8.02 (dd, *J* = 8.6, 1.8 Hz, 1H), 7.99 (dd, *J* = 7.0, 1.4 Hz, 1H), 7.89 (d, *J* = 8.2 Hz, 1H), 7.86 (d, *J* = 7.9 Hz, 1H), 7.67 (s, 2H), 7.58 (d, *J* = 9.0 Hz, 2H), 7.50 (dqd, *J* = 8.5, 6.9, 1.6 Hz, 2H), 6.67 (d, *J* = 9.0 Hz, 2H), 2.93 (s, 6H). ^{13}C NMR (75 MHz, d_6-acetone) δ 188.9,152.8,145.4,136.9,135.8,133.3,130.9,129.9,129.8,128.6,128.5,128.1,127.0, 124.9, 123.1, 116.7, 112.2, 39.7.

Syntesis of (*E*)-1,3-bis(4-(dimethylamino)phenyl)-1-(naphthalene-2-yl)prop-2-en-1-ol (1). *N*,*N*,*N*',*N*'-tetramethylethylenediamine (332 µL, 2.18 mmol) was dissolved in ethyl ether (20 mL) under inert atmosphere. Then, *n*-butyllithium (1.3M in hexane, 1.68 mL, 2.18 mmol) was added to the previously prepared solution and the mixture was stired for 45 to form the BuLi-TMEDA complex. Then 4-bromo-N,N-dimethylaminoaniline (451 mg, 2.18 mmol) in diethyl ether (10 ml) was added to the BuLi-TMDA complex. After 45 min. at room temperature, *p*-dimethylaminenaphthylidenketone (**4**) (327 mg, 1.09 mmol) dissolved in THF (30 mL) was added to the and the mixture was stirred for 5 hours at room temperature. Then, the reaction was poured in water (100 mL) and the aqueous phase was extracted with dichloromethane (3 × 20 mL). The organic phase was washed with brine (20 mL), dried with anhydrous $MgSO_4$ and evaporate to give a yellow oil. The oil was stirred with hexane to afford **1** as a green solid (220 mg, 48%). m. p. 133ºC. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.91 (d, *J* = 1.7 Hz, 1H), 7.77 - 7.67 (m, 4H), 7.42 (dd, *J* = 8.6, 1.8 Hz, 1H), 7.40 - 7.35 (m, 2H), 7.23 (dd, *J* = 8.9, 3.6 Hz, 4H), 6.62 - 6.57 (m, 5H), 6.46 (d, *J* = 15.9 Hz, 1H), 2.87 (s, 6H), 2.86 (s, 6H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 150.6, 150.2 , 144.6 , 134.7, 133.5 , 132.8,131.8 , 129.6, 128.7, 128.6 , 128.1 , 128.0 , 127.9, 126.4, 126.3, 126.3 , 126.2 , 125.7, 125.3, 112.8 , 112.5 , 79.9 , 41.0. HRMS (EI): m/z calc. for $C_{29}H_{29}N_2$ $[M\text{-}OH]^+$: 405.2331 $[M\text{-}OH]^+$ found: 405.2334.

Synthesis of 1,1-bis(4-(dimethylaminephenyl-3-phenylprop-2-in-1-ol (2)[8]**.** Phenylacetilene (200 µL, 1.82 mmol) was dissolved in freshly distilled THF (15 mL) and the solution was kept under inert atmosphere. Then, BuLi (1.32 M in hexane, 1.52 mL, 1.1 equiv.) was added to the solution and the mixture was stirred for 25 minutes. After this, 4,4'-bis(dimethylamine)benzophenone (488 mg, 1.82 mmol) dissolved in dry THF (10 mL) was added at 0 ºC. The reaction was kept at room temperature overnight and then water (50 mL) was added to obtain a white-yellow solid. The product was purified by column chromatography on silica gel (hexane:ethyl acetate:Et_3N 8:3:1) to yield **2** (296 mg, 44%). ^{1}H NMR (300 MHz, acetone) δ 7.39 - 7.30 (m, 6H), 7.27- 7.21 (m, 3H), 6.56 (d, *J* = 9.0 Hz, 4H), 2.77 (s, 12H). ^{13}C NMR (75 MHz, acetone) δ 150.3, 135.2, 132.0, 131.7, 128.9, 128.6, 127.3, 112.2, 94.7, 85.2, 73.7, 40.2. HRMS (EI): m/z calc. for $C_{25}H_{27}N_2O$ $[M+H]^+$: 371.2123 $[M+H]^+$ found: 371.2119.

Synthesis of (*E*)-3-(4-(dimethylamine)phenyl-1-(naphthalene-2-yl)prop-2-en-1-ol (3). *p*-Dimethylaminenaphthylideneketone (**4**) (50 mg, 0.166 mmol) was dissolved in MeOH (10 mL). Then, $NaBH_4$ (63 mg, 1.66 mmol) was added in small portions to this solution and the mixture was stirred at room temperature overnight. Finally, water (20 mL) was added to the solution and it was extracted with dichloromethane (3 × 20 mL). The organic phase was washed with brine (20 mL), dried with anhydrous $MgSO_4$ and evaporated to give **3** as a dark oil (47 mg, 93%). ^{1}H NMR (300 MHz, acetone) δ 8.02 (d, *J* = 0.7 Hz, 1H), 7.93 - 7.86 (m, 3H), 7.66 (dd, *J* = 8.6, 1.7 Hz, 1H), 7.49 (pd, *J* = 6.8, 1.8 Hz, 2H), 7.32 (d, *J* = 8.8 Hz, 2H), 6.74 - 6.65 (m, 3H), 6.33 (dd, *J* = 15.8, 6.8 Hz, 1H), 5.57 (d, *J* = 6.8 Hz, 1H), 4.76 (s, 1H), 2.89 (s, 6H). ^{13}C NMR (75 MHz, acetone) δ 150.7 , 142.9 , 134.0 , 133.3 , 130.4 , 128.9 , 128.4 , 128.3 , 128.1 , 127.9 , 126.4 , 126.0, 125.6 , 125.6, 124.9, 112.8, 75.3, 40.1. HRMS (EI): m/z calc. for $C_{21}H_{20}N$ $[M\text{-}OH]^+$: 286.1590 $[M\text{-}OH]^+$ found: 286.1596.

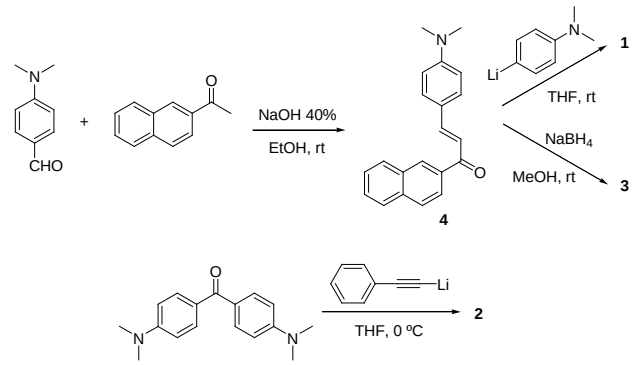
General procedure for Detection-limit Determinations. To the corresponding carbinol dissolved in acetonitrile, increasing amounts of the corresponding simulant solution (DFP and DCNP) were added. UV-visible spectra were recorded in 1 cm path length cells at 20ºC (thermostated). Representation of absorbance at the appropriate wavelength versus concentration of the simulant allows the calculation of the detection limits.

Regeneration experiments. 10 µL of DCNP were added to 10 mL of a 9.0 x 10^{-4} mol dm^{-3} solution of carbinol **3** in H_2O/MeCN (99/1) and the solution was kept stirring at room temperature during 2 minutes. After this time the UV spectrum of the solution was registered. Then 1M TBAOH in MeOH was added until the solution fades. The solution was kept stirring for 30 seconds and then the process was started again.

Results and discussion

Compounds **1**-**3** were prepared following the pathways described in Scheme 3. For the preparation of **1** and **3**, first 4-(*N*,*N*-dimethylaminino)benzaldehyde was condensed with 2-acetylnaphthalene in order to obtain the intermediate ketone **4**.[9] The reaction of this ketone with 4-(*N*,*N*,-dimethylamino)phenyllithium yielded compound **1**

(48%),[10] whereas reduction of the same ketone allowed us to obtain compound **3** with 93% yield. Finally, derivative **2** was prepared from 4,4'-bis(dimethylamino)benzophenone by reaction with lithium phenylacetilure (44%).[11]



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Scheme 3 Synthetic procedure for the preparation of carbinols **1**-**3**

The prepared compounds **1**-**3** can be converted in their corresponding cations **1a**-**3a** (see Scheme 2) by reaction with perchloric acid. Table 1 shows the absorption bands observed for these compounds in acetonitrile. As can be seen the transformation of the carbinols in the corresponding carbocation results in a significant bathochromic shift. Thus, whereas the carbinols show absorption maxima in the UV zone (i.e. λ_{max} = 274, 266, 284 nm for **1**, **2** and **3**, respectively), the corresponding carbocations display absorption bands in the visible range (i.e. 715, 689 and 510 nm for **1a**, **2a** and **3a**, respectively). Moreover, the trisubstituted cations **1a** and **2a** show absorption bands at longer wavelengths than cation **3a** which only contains two aromatic substituents.

Table 1. Maxima of the UV-visible spectra of carbinols **1**-**3** and their corresponding carbocations **1a**-**3a** in acetonitrile (1.0 x 10^{-5} mol dm^{-3}).

Probe	**1**	**2**	**3**	**1a**	**2a**	**3a**
λ (nm)	274	266	284	715	689	510

Signalling studies were carried out with diethylcyanophosphonate (DCNP) and diisopropylfluorophosphate (DFP) in acetonitrile (see Scheme 4 for its structures). Arising from the high toxicity of the nerve agents, Sarin, Soman and Tabun,[12] the related compounds DFP and DCNP have been typically used as models for the design of indicators and sensing systems, as they have similar reactivity but lack their acute toxicity. Initially studies were carried out with compound **1** in acetonitrile (1.0 x 10^{-5} mol dm^{-3}) which displays an absorption band at 274 nm. The addition of DFP or DCNP to acetonitrile solutions of **1** resulted in the appearance of a new absorption band at 715 nm (Figure 1) and colour modulation from colourless to blue. The observed results are fully consistent with the phosphorylation and subsequent elimination shown in Scheme 1.

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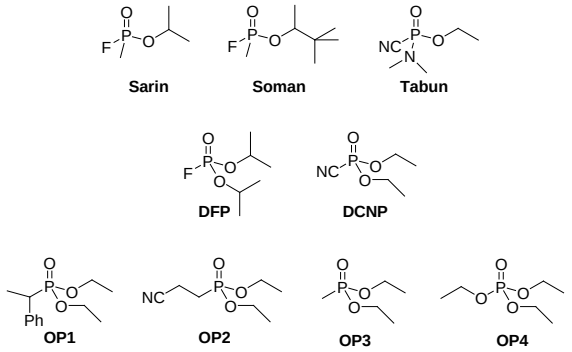

Scheme 4 Chemical structure of nerve agents (sarin, soman and tabun), its simulants (DFP and DCNP) and the organophosphonates used for the interference assay

Nearly the same spectroscopic behaviour was observed upon addition of DFP and DCNP to acetonitrle solutions of carbinols **2** and **3**, namely the apparition of a red shifted absorption band (689 and 510 nm for **2** and **3** respectively) due to the formation of the correspondent carbocation (data not shown). These red shifted absorptions were the responsible of the colour changes observed with probe **2** (colourless solution of this carbinol turned green-blue upon addition of DFP and DCNP, see Figure 2), and with carbinol **3** (the colourless initial acetonitrile solution turned pink upon addition of both simulants, data not shown).

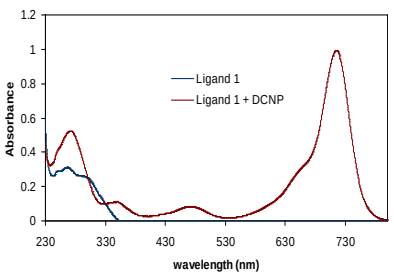

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Fig. 1 UV-visible spectra of carbinol **1** alone and in the presence of 100 equiv. of DCNP in acetonitrile (1.0 x 10^{-5} mol dm^{-3})

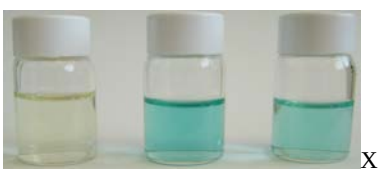

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Fig. 2 Colour changes observed for probe **2** (1.0 x 10^{-5} mol dm^{-3}) in acetonitrile upon addition of 100 equivalents of DCNP (middle) and 100 equivalents of DFP (right)

In a second step, and in order to evaluate the applicability of these carbinols for the detection of nerve agent simulants, the limits of detection (LOD) for the three carbinols were determined. At this respect, LOD for probes **1**, **2** and **3** in the presence of DCNP and DFP are summarized in Table 2. Compounds **2** and **3** showed lower LOD values for DCNP than for DFP in agreement with the trend observed using other chromoreagents.[4c,5a] However, this tendency was the opposed for compound **1**. Moreover, it is also evident form Table 2 that trisubstituted carbinols (i.e. **1** and **2**) gave lover detection limits than the

corresponding disubstituted carbinol **3**. Finally, it is also apparent from Table 2 that lower detection limits were observed for probe **1** when compared with **2** and **3**.

Finally, the reactivity of carbinols **1**-**3** with other organophosphorous compounds (**OP1**-**OP4**) (*C* = 250 equiv.) shown in Scheme 4 was studied in acetonitrile. In all cases, the solutions of carbinols **1**-**3** remained colorless, which indicated that no reaction occurred between them and these phosphate derivatives. The lack of response of carbinols **1**-**3** in the presence of **OP1**-**OP4** is clearly related with the absence of a good leaving group in the structure of the latter. The impossibility of phosphorylation reaction precludes the formation of the highly coloured carbocations **1a**-**3a**.

Table 2. Limit of detection, LOD (ppm) and kinetic data for probes **1**-**3** with DCNP and DFP (1.0 x 10^{-5} mol dm^{-3} in acetonitrile)

Probe	Simulant	Detection limit (ppm)	k (s^{-1})	$t_{1/2}$ (s)
1	DFP	35	0.0230	30.2
	DCNP	85	0.0144	48.2
2	DFP	264	0.0025	277.3
	DCNP	165	0.0026	266.6
3	DFP	1700	0.0013	533.2
	DCNP	268	0.0010	693.2

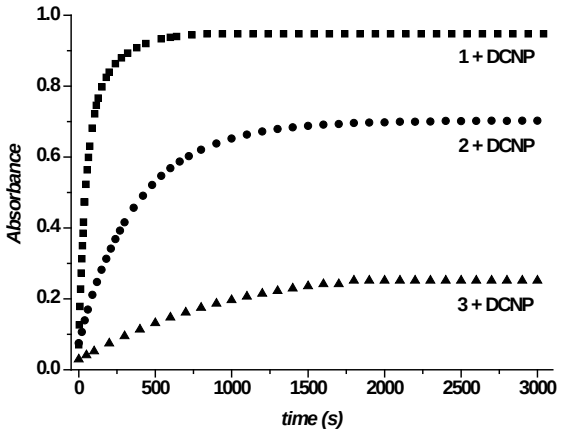

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Fig. 3 Changes in the absorbance band (visible zone) vs. time for carbinols **1**-**3**, in acetonitrile (1.0 x 10^{-5} mol dm^{-3}), upon addition of 100 equiv. of DCNP

To achieve a better understanding of the reaction, studies of the reactivity of compounds **1**-**3** in the presence of the mimics DCNP and DFP in acetonitrile solutions, by using an excess of the corresponding simulant to ensure to be under pseudofirst order conditions, were carried out. Monitorization of the changes in the absorbance intensity of the carbocation band and the plotting of $\ln[(A_0-A)/A_0]$ versus time (being A_0 the final absorbance, and A the absorbance at a given time), allowed us the determination of the rate constant (*k*) and the half time ($t_{1/2} = \ln 2/k$) for the corresponding reaction of the nerve-gas simulants with the probes. For example, the absorbance changes at the UV/Vis band maximum for acetonitrile solutions of probes **1**, **2** and **3** in the presence of DCNP is shown in Figure 3. The kinetic data are summarized in Table 2. The obtained data showed that the reaction of the simulants DCNP and DCP with probe **1** is quicker than with **2** and **3**.

The detection of DCNP or DFP using compounds **1**, **2** and **3** follow a chemodosimeter approach in which the presence of the analyte is signalled through a specific chemical reaction between dosimeter molecule and the target species, leading to the formation of a fluorescent or coloured product. An advantage of this approach is the remarkable selectivity usually achieved, however a disadvantage of dosimeters is that in most cases the reactions are irreversible and thus provide only single-use assays. However, in certain circumstances, it is possible to take advantage of the favourable features of chemodosimeters and also reuse them.

One particular feature of the formation of arylcations from the corresponding arylcarbinols is that the process can be reversed and it has been reported that in the presence of hydroxide the arylcarbinol derivatives could be retrieved.[13] Therefore the attractive possibility of attaining re-usable colorimetric probes was tested via recuperation of the sensing arylcarbinol by reaction of the arylcation derivative with basic solutions. Thus, after having accomplished the reaction between the probes **1**-**3** and the simulants, the carbinols obtained (**1a**-**3a**) were treated with TBAOH. Upon this treatment, the probes **1**-**3** were fully regenerated and could be used for another measurement. Taking this reaction into account the possible use of the prepared chemodosimeter in subsequent sensing cycles has been explored. Figure 4 shows the absorbance at 510 nm for probe **3** in the presence of DCNP after successive regeneration cycles. After 10 cycles probe **3** is still able to display colour modulations in the presence of nerve agent simulants. The same regeneration cycles were applied to carbinols **1** and **2** and are also able to display colour modifications upon addition of DCNP (data not shown).

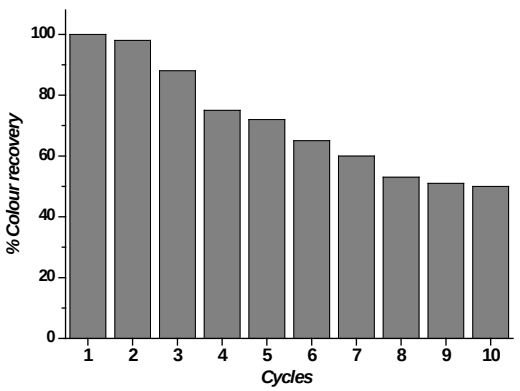

Fig. 3 Absorbance of the 510 nm band upon consecutive exposure of probe **3** to DCNP in acetonitrile. After each reaction probe **3** is retrieved by treatment of the corresponding carbocation **3a** with TBAOH

Conclusions

In summary, a family of new reagents for the chromogenic detection of nerve agent simulants has been prepared. The sensing protocol relies in the reactivity of the nerve agent simulants with arylcarbinols to produce, upon phosphorylation and elimination, the corresponding highly coloured arylcations. Additionally the synthesis of the arylcarbinols is easy and the approach is highly modular bearing in mind that a number of chemical modifications can be carried out on the probes that might result in a modulation of their reactivity with the nerve agent simulants and also a modulation in the chromogenic response. In all cases the reaction of the probes with the nerve agent mimics result in remarkable off-on chromogenic behaviours. It is also noteworthy that these reagents react only with DFP and DCNP that show close chemical structures to Sarin, Soman and Tabun, whereas they do not react with other organophosphorous derivatives such as **OP1**-**OP4**. Moreover the fact that the probes retain their signaling ability upon regeneration with TBAOH is an additional issue of interest.

Acknowledgments

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Notes and references

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† Electronic Supplementary Information (ESI) available: [Spectral data ^{1}H and ^{13}C NMR spectra. UV and changes color of ligand **2** and **3** in presence of DCNP]. See DOI: 10.1039/b000000x/

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