New Efficient Approach for the Synthesis of 2-Alkyl(aryl) Substituted 4*H*-Pyrido[1,2-*a*]pyrimidin-4-ones

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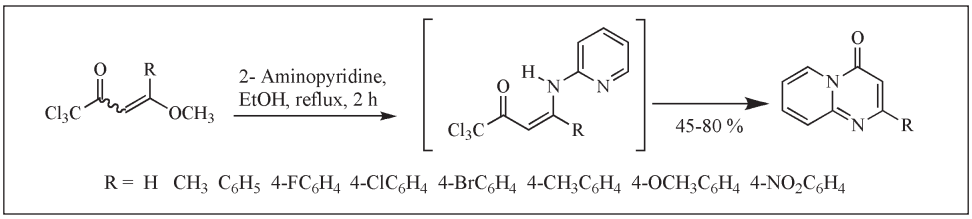

A new, efficient and easy route for the preparation of a series of 2-alkyl(aryl) substituted 4-oxo-4*H*-pyrido-[1,2-*a*]pyrimidines, where alkyl = CH_3; aryl = C_6H_5, 4-FC_6H_4, 4-ClC_6H_4, 4-BrC_6H_4, 4-$CH_3C_6H_4$, 4-OCH_3-C_6H_4, 4-$NO_2C_6H_4$ in 45 – 80 % yield from the reaction of β-alkoxyvinyl trichloromethyl ketones with 2-aminopyridine under mild conditions, is then reported.

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In the last years, the introduction of a trifluoro- or trichloromethyl group into an acyclic or cyclic compound have widely been studied and reviewed [1,2]. Consequently, these new organic structures can bring about remarkable changes in their physical, chemical and biological properties.

Recently, we have also reported an addition/elimination sequence leading to trifluoroacetyl and trichloroacetyl acyclic enamines from the reaction of *o*-phenylenediamine [3], *o*-aminophenol [4], 1-naphthylamine [5] and S,S-dimethylsulfoximide [6] with 4-alkyl(aryl)-1,1,1-trihalo-4-alkoxyalken-2-ones. The acyclic enaminones, derived from *o*-phenylenediamine and *o*-aminophenol, were submitted to *in vitro* anti-tumor screens. It was observed that the trichloromethylated compounds exhibited a superior activity if compared to trifluoromethylated analog compounds. The best activity was obtained when the structure was derived from *o*-aminophenol and it presents a trichloroacetyl- and a *p*-bromophenyl substituent bound at the carbon-2 and -1, respectively [4].

β-Alkoxyvinyl trichloromethyl ketones **1** proved also to be useful building blocks for the synthesis of five-, six-, and seven-, member trichloromethylated heterocycles [2] due to the fact that one of the best methods to introduce a trichloromethyl group into heterocycles is based on the trichloromethylated building block approach. This approach relies on the trichloroacetylation of enol ethers or acetals to give, in one step and good yields, the above cited ketones **1**. On the other hand, the classical haloform reaction in which the trichloromethyl substituent is a leaving group is well developed [7] and systematic studies, involving the usefulness of the leaving group ability of the trichloromethyl in many synthetic transformations, were reported [2,8-14]. However, just a few references from the literature report the use of the trichloromethyl substituent as a good leaving group in heterocyclic synthesis [15]. Furthermore, the synthetic strategy involving the ketones **1** and 2-aminopyridine was never applied in attempt to obtain regiospecificaly 2-alkyl(aryl)substituted 4*H*-pyrido[1,2-*a*]pyrimidin-4-ones under relative mild conditions.

Although some researches, up to 1951, considered that the heterocycle obtained from the reaction of 2-aminopyridine with ethyl acetoacetate was 4-methyl-2*H*-pyrido[1,2-*a*]pyrimidin-2-one, Antaki and Petrow [16] showed (in 1951), that the product was, in fact, the 2-methyl-4-keto isomer. To prove this hypothesis, 2-methyl-4*H*-pyrido[1,2-*a*]pyrimidin-4-one was obtained from the reaction of 2-bromopyridine with ethyl β-aminocrotonate at 180 – 200 ºC for 5 – 6 hours in the presence of copper bronze and anhydrous potassium carbonate or when 2-aminopyridine and ethyl β-aminocrotonate were heated together at 160 – 180 ºC for 6 – 8 hours. In 1968, Shur and Israelstam [17] showed that pyrido[1,2-*a*]pyrimidin-4-ones can be obtained in a one-stage process by condensing methyl- or halo-substituted 2-aminopyridines with β-keto esters in the presence of PPA. Optimum yields (> 80%) were obtained by heating the 2-aminopyridines with β-keto esters at 100 ºC for about 1 hour together with four- to sixfold quantity of PPA. Four years before, Kato *et al*. [18] synthesized 2-methyl-4*H*-pyrido[1,2-*a*]pyrimidin-4-one by treating 2-aminopyridine with diketene in only 28 % yield.

In 1972, Mendel [19] synthesized, by a new method but in low yields, 2-methyl- (35 %) and 2-phenyl-4*H*-

pyrido[1,2-*a*]pyrimidin-4-one (20 %) from the reaction of 2-aminonicotinic acid with ethyl acetoacetate or ethyl benzoylacetate, respectively.

In 1977, Hermecz *et al*. [20] reported that 3-, 6- and 8-substituted 4*H*-pyrido[1,2-*a*]pyrimidin-4-ones can be obtained from the ring closure reactions of 2-substituted 3-(2-pyridylamino)acrylates in a mixture of phosphoryl chloride and PPA at 130 ºC in 40 -96 % yields.

In 2002, a series of 6(8)-methyl-, 7(9)-halo-, 8(9)ethyl- and 8-nitro-substituted 4*H*-pyrido[1,2-*a*]pyrimidin-4-ones [21] were obtained in 21 - 74 % yields, when the pyridylaminomethylene malonates synthesized from the reactions of ethoxymethyleneisopropylidene malonate with 2-aminopyridines were heated to their melting points. Previously, 7-alkyl substituted pyridopyrimidines analogs [22] were isolated from the 2-pyridylamino- or 5-methyl-2-pyridylaminomethyleneisopropylidene malonates by also melting them.

Since 1983, the interesting and non-substituted 4*H*-pyrido[1,2-*a*]pyrimidin-4-one has only been synthesized by laborious procedures involving a mixture of Meldrum's acid, trimethyl orthoformate and 2-aminopyridine [23] or from the reaction of ethyl *N*-(2-pyridyl) formimidate with ketene in 58 % yield [24].

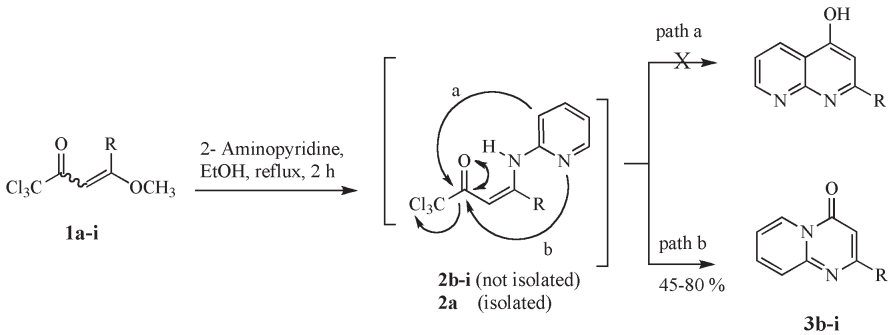
Parallel to the growing interest in the synthesis of pyrido[1,2-*a*]pyrimidin-4-ones to provide biologically active molecules, a large number of publications showed that several derivatives of them appeared as tranquilizer [25], antiallergic [26], antiulcerative [27], antiasthmatic [28] and bronchodilator agents [29] or showing analgesic activity [30] and human platelet aggregation inhibitory properties [31].

As an extension of our research we wish to report the discovery of a new and easy route for the preparation of a series of 2-alkyl(aryl)substituted 4-oxo-4*H*-pyrido[1,2-*a*]pyrimidines **3** from the reaction employing β-alkoxyvinyl trichloromethyl ketones **1** and 2-aminopyridine (Scheme 1), when mild conditions were used to obtain the respective trichloroacetyl enamines **2**.

The 4-alkyl(aryl)-1,1,1-trichloro-4-alkoxy-alk-3-en-2-ones (**1**) are readily available *CCC* synthetic blocks and were prepared from trihaloacetylation of enol ethers (**1a-b**) [32] or from enol ethers generated *in situ* from the respective acetophenone acetals (**1c-i**) [33,34] with trichloroacetyl chloride. The most satisfactory results of these reactions, selected physical and elemental analyses are recorded in Table 1 and spectral data are presented in the experimental part.

We have attempted to obtain the enamino ketone intermediate *N*-[1-alkyl(aryl)-3-oxo-4,4,4-trichloroalk-1-en-1-yl]-2-aminopyridines (**2**) by the reaction of β-alkoxyvinyl trichloromethyl ketones **1** with 2-aminopyridine. When these reactions were carried out in dichloromethane as solvent, the respective enamino ketones were isolated in a very low yield (> 10%). Surprisingly, when the same reactions were carried out in a molar ratio of 1:1 respectively, in anhydrous ethanol as solvent under reflux for 5 hours, 2-substituted 4-oxo-4*H*-pyrido[1,2-*a*]pyrimidines (**3b-i**) were easily isolated in 45 – 81% yields. Except for reaction involving **1a**, the above described conditions allowed us to obtain regiospecificaly pyrido[1,2-*a*]pyrimidin-4-ones (Scheme 1, path b) instead 5-trichloromethyl-1,8-naphthyridines (Scheme 1, path a) or their 4-substitued 2-keto-pyridopyrimidine isomer. Although, similar conditions were employed to synthesize 5*H*-thiazolo[3,2-*a*]pyrimidin-5-ones previously [18c], we have found in this case an unexpected reactivity of the endocyclic nitrogen atom of the π-deficient pyridine ring towards the carbonyl group of the β-alkoxyvinyl trichloromethyl ketones. Although, the 4*H*-pyrido[1,2-*a*]pyrimidin-4-one was synthesized previously [23,24], unfortunately reactions of *N*-[3-oxo-4,4,4-trichlorobut-1-en-1-yl]-2-aminopyridine (**2a**) in refluxing ethanol, *n*-butanol or acidic media as sulfuric acid or PPA at reflux or using $TiCl_4$ as catalysts at different temperatures in an attempt to obtain the respective cyclic structure, resulted always in the recovery of precursor (**2a**)

Scheme I



1-3	a	b	c	d	e	f	g	h	i
R	H	CH_3	C_6H_5	4-FC_6H_4	4-ClC_6H_4	4-BrC_6H_4	4-$CH_3C_6H_4$	4-$OCH_3C_6H_4$	4-$NO_2C_6H_4$

or complex mixtures of non identified products by ^{1}H- and ^{13}C-NMR spectroscopy are produced. However, the isolation of the trichloroacetyl enamine **2a** demonstrates also that the pyrido[1,2-*a*]pyrimidinone system (**3b-i**) must be the 4-keto isomer.

Table 1

Selected physical and elemental analyses data of *N*-[1-alkyl(aryl)-3-oxo-4,4,4-trichlorobut-1-en-1-yl]-2-aminopyridine(**2a**) and 2-Alkyl(aryl)-4*H*-pyrido[1,2-*a*]pyrimidin-4-ones (**3b-i**).

Compds. (R Substituent)	Yield (%)[a]	Mp (°C)[b]	Molecular Formula (g/mol)	Elemental Analyses (%) Calcd. / Found		
				C	H	N
2a	62	110 – 111	$C_9H_7Cl_3N_2O$	40.71	2.66	10.55
(H)			265.53	40.86	2.70	10.73
3b	66	118 – 119	$C_9H_8N_2O$	67.49	5.03	17.49
(CH_3)	[96] [c]	[123 – 124] [c]	160.18	-	-	-
3c	81	144 – 145	$C_{14}H_{10}N_2O$	75.66	4.54	12.60
(C_6H_5)	[20][c]	[147 – 148] [c]	222.25	-	-	-
3d	65	201 – 202	$C_{14}H_9FN_2O$	70.00	3.78	11.66
(4-FC_6H_4)			240.24	69.88	3.90	11.49
3e	68	203 – 204	$C_{14}H_9ClN_2O$	65.51	3.53	10.91
(4-ClC_6H_4)			256.69	65.27	3.67	10.85
3f	71	200 – 201	$C_{14}H_9BrN_2O$	55.84	3.01	9.30
(4-BrC_6H_4)			301.14	55.55	3.14	9.06
3g	70	161 – 163	$C_{15}H_{12}N_2O$	76.25	5.12	11.86
(4-$CH_3C_6H_4$)			236.27	75.96	4.99	11.63
3h	45	157 – 158	$C_{15}H_{12}N_2O_2$	71.42	4.79	11.10
(4-$CH_3OC_6H_4$)			252.27	71.25	4.91	10.98
3i	55	217 – 218	$C_{14}H_9N_3O_3$	62.92	3.39	15.72
(4-$NO_2C_6H_4$)			267.24	63.03	3.55	15.83

[a] Yields of isolated compounds; [b] Melting points are uncorrected; [c] Known compounds (**3b**, ref. 17; **3c**, ref. 24).

In summary, it was observed that the reactions of β-alkoxyvinyl trichloromethyl ketones (**1**) with 2-aminopyridine carried out in anhydrous ethanol under reflux give the intermediates *N*-[1-alkyl(aryl)-3-oxo-4,4,4-trichloroalk-1-en-1-yl]-2-aminopyridines **2**, which were not isolated, except for **2a**. Thus, the intermediates **2** act as N-heterocyclic acylating agent enabling to present a new, simple, and convenient method to obtain substituted 4-oxo-4*H*-pyrido[1,2-*a*]pyrimidines (**3**) in good yields.

EXPERIMENTAL

Unless otherwise indicated all common reagents and solvents were used as obtained from commercial suppliers without further purification. All melting points were determined on an Electrothermal Melt-Temp 3.0 apparatus and are uncorrected. ^{1}H and ^{13}C NMR spectra were acquired on a Bruker DPX 200 spectrometer (^{1}H at 200.13 MHz and ^{13}C at 50.32 MHz), 5 mm sample tubes, 298 K, digital resolution ±0.01 ppm, in chloroform-d_1 using TMS as internal reference. Mass spectra were registered in a HP 6890 GC connected to a HP 5973 MSD and interfaced by a Pentium PC. The GC was equipped with a split-splitless injector, autosampler, cross-linked HP-5 capillary column (30m, 0.32mm of internal diameter), and helium was used as the carrier gas. The CHN elemental analyses were performed on a Perkin Elmer 2400 CHN elemental analyzer (São Paulo University – USP / Brazil).

General Procedure for the Preparation of *N*-[3-Oxo-4,4,4-trichlorobut-1-en-1-yl]-2-aminopyridine (**2a**).

To a stirred solution of 4-ethoxy-1,1,1-trichloro-3-buten-2-one **1a** (5 mmoles) in 15 ml of anhydrous ethanol, 2-aminopyridine (5 mmoles) was added at 20 – 25 °C. The mixture was stirred for 5 hours at 80 – 85 °C (oil bath). After the reaction time, the solvent was evaporated under reduced pressure and the crude products **2a** purified by recrystallization from ethyl acetate.

This compound was obtained as yellow solid, yield 62 %, Mp. 110 - 111 ºC. ^{1}H NMR ($CDCl_3$) δ= 11.27 (bs, 1H, NH), 8.44 (dd, *J*= 12.4, *J*= 8.3, 1H, H-1'), 8.33 (d, *J*= 3.6, 1H, PyH-6), 7.66 (m, 1H, PyH-4), 7.04 (m,1H, PyH-5), 6.85 (d, *J*= 8.0, 1H, PyH-3), 6.04 (d, *J*=8.3, 1H, H-2'). ^{13}C NMR ($CDCl_3$) δ = 183.4 (C=O), 150.5 (PyC-2), 148.7 (C-1'), 147.3 (PyC-6), 138.7 (PyC-4), 119.7 (PyC-3), 111.9(PyC-5), 96.3 (CCl_3), 89.6 (C-2'). GC/MS (EI, 70 eV): *m/z* (%) = 264 (M^+, 10), 165 (24), 201 (17), 147 (100), 119 (80), 78 (93), 51 (25).

General Procedure for the Preparation of 2-Alkyl(aryl)-4*H*-pyrido[1,2-*a*]pyrimidin-4-ones (**3b-i**).

To a stirred solution of 4-alkoxy-4-alkyl(aryl)-1,1,1-trichloro-3-buten-2-one **1b-i** (5 mmoles) in 15 ml of anhydrous ethanol, 2-aminopyridine (5 mmoles) was added at 20 – 25 °C. The mixture was stirred for 5 hours at 80 – 85 °C (oil bath). After the reaction time, the solvent was evaporated under reduced pressure and the crude products **3b** purified by recrystallization from a mixture of ethyl acetate and *n*-hexane (3:1). Compounds **3c-i** precipitated after the reaction time and were isolated by filtration and purified by recrystallization from a mixture of ethanol and *n*-hexane (3:1).

2-Methyl-4*H*-pyrido[1,2-*a*]pyrimidin-4-ones (**3b**).

This compound was obtained as white solid, yield 66 %, Mp. 118 -119 ºC. ^{1}H NMR ($CDCl_3$) δ = 9.03 (d, J=7.1, 1H, H-6), 7.73 (t, J=7.6, 1H, H-7), 7.59 (d, J=8.8, 1H, H-9), 7.12 (t, J=7.0, 1H, H-8), 6.34 (s, 1H, H-3), 2.47 (s, 3H, CH_3). ^{13}C NMR ($CDCl_3$) δ = 165.0 (C-2), 157.5 (C-4), 150.5 (C-9a), 136.0 (C-7), 126.9 (C-6), 125.5 (C-9), 114.8 (C-8), 103.0 (C-3), 24.4 (CH_3). GC/MS (EI, 70 eV): *m/z* (%) = 160 (M+, 57), 131(100), 78 (75), 51 (41).

2-Phenyl-4*H*-pyrido[1,2-*a*]pyrimidin-4-ones (**3c**).

This compound was obtained as yellow solid, yield 81 %, Mp. 144 - 145 ºC. ^{1}H NMR ($CDCl_3$) δ = 9.06 (d, *J*=7.1, 1H, H-6), 8.09 (m, 2H, Ph), 7.75 (m, 2H, Ph), 7.49 (m, 3H, Ph, H-7, H-9), 7.13 (m, 1H, H-8), 6.91 (s, 1H, H-3). ^{13}C NMR ($CDCl_3$) δ = 161.7 (C-2), 158.3 (C-4), 150.8 (C-9a), 137.0 (Ph), 135.9 (C-7), 130.4 (C-6), 128.5 (Ph), 127.2 (Ph), 127.0 (Ph), 126.3 (C-9), 114.9 (C-8), 99.7 (C-3). GC/MS (EI, 70 eV): *m/z* (%) = 222 (M^+, 97), 194 (100), 78 (88), 51 (43).

2-(4-Fluorophenyl)-4*H*-pyrido[1,2-*a*]pyrimidin-4-ones (**3d**).

This compound was obtained as white solid, yield 65 %, Mp. 201 - 202 ºC. ^{1}H NMR ($CDCl_3$) δ = 9.05 (d, J=7.0, 1H, H-6), 8.10 (t, 2H, Ph), 7.75 (d, 2H, Ph), 7.17 (t, 2H, Ph, H-7, H-9), 7.13 (m, 1H, H-8), 6.84 (s, 1H, H-3). ^{13}C NMR ($CDCl_3$) δ = 164.5 (d, ^1J= 251.4, F-Ph), 160.7 (C-2), 158.3 (C-4), 150.9 (C-9a), 136.4 (C-7), 133.1 (d, ^4J=2.8, F-Ph), 129.5 (d, ^3J=9.1, F-Ph), 127.3 (C-6), 126.5 (C-9), 115.7 (d, ^2J=21.1, F-Ph), 115.2 (C-8), 99.5 (C-3). GC/MS (EI, 70 eV): *m/z* (%) = 240 (M^+, 47), 212 (100), 78 (65), 51 (20).

2-(4-Chlorophenyl)-4*H*-pyrido[1,2-*a*]pyrimidin-4-ones (**3e**).

This compound was obtained as white solid, yield 68 %, Mp. 203 - 204 ºC. ^{1}H NMR ($CDCl_3$) δ = 9.07 (d, *J*=7.0, 1H, H-6), 8.03 (d, *J*=8.8, 2H, Ph), 7.75 (m, 2H, H-7, H-9), 7.47 (d, *J*=8.8, 2H, Ph), 7.15 (m, 1H, H-8), 6.88 (s, 1H, H-3). ^{13}C NMR ($CDCl_3$) δ = 160.5 (C-2), 158.3 (C-4), 150.9 (C-9a), 136.7 (Ph), 136.2 (C-7), 135.5 (Ph), 128.9 (Ph), 128.6 (Ph), 127.2 (C-6), 126.6 (C-9), 115.2 (C-8), 99.7 (C-3). GC/MS (EI, 70 eV): *m/z* (%) = 256 (M^+, 47), 228 (100), 78 (73), 51 (33).

2-(4-Bromophenyl)-4*H*-pyrido[1,2-*a*]pyrimidin-4-ones (**3f**).

This compound was obtained as white solid, yield 71 %, Mp. 200 - 201 ºC. ^{1}H NMR ($CDCl_3$) δ = 9.05 (d, *J*=7.2, 1H, H-6), 7.96 (d, *J*=8.5, 2H, Ph), 7.75 (m, 2H, H-7, H-9), 7.62 (d, *J*=8.6, 2H, Ph), 7.14 (m, 1H, H-8), 6.86 (s, 1H, H-3). ^{13}C NMR ($CDCl_3$) δ = 160.6 (C-2), 158.4 (C-4), 151.0 (C-9a), 136.4 (C-7), 135.9 (Ph), 131.9 (Ph), 128.9 (Ph), 127.3 (C-6), 126.6 (C-9), 125.3 (Ph), 115.3 (C-8), 99.8 (C-3). GC/MS (EI, 70 eV): *m/z* (%) = 301 (M^+, 47), 272 (85), 78 (100), 51 (49).

2-(4-Toluyl)-4*H*-pyrido[1,2-*a*]pyrimidin-4-ones (**3g**).

This compound was obtained as yellow solid, yield 70 %, Mp. 161 - 163 ºC. ^{1}H NMR ($CDCl_3$) δ = 9.01 (d, *J*=7.0, 1H, H-6), 7.97 (d, *J*=8.2, 2H, Ph), 7.67 (m, 2H, H-7, H-9), 7.27 (d, *J*=8.0, 2H, Ph), 7.05 (m, 1H, H-8), 6.86 (s, 1H, H-3), 2.39 (s, 3H, CH_3). ^{13}C NMR ($CDCl_3$) δ = 161.6 (C-2), 158.3 (C-4), 150.6 (C-9a), 140.7 (C-7), 135.9 (Ph), 134.0 (Ph), 129.2 (Ph), 127.0 (Ph), 126.9 (C-6), 126.3 (C-9), 114.8 (C-8), 99.1 (C-3), 21.2 (CH_3). GC/MS (EI,70 eV): *m/z* (%) = 236 (M^+ , 66), 208 (100), 78 (32), 51 (11).

2-(4-Methoxyphenyl)-4*H*-pyrido[1,2-*a*]pyrimidin-4-ones (**3h**).

This compound was obtained as white solid, yield 45 %, Mp. 157 - 158 ºC. ^{1}H NMR ($CDCl_3$) δ = 9.04 (d, *J*=7.0, 1H, H-6), 8.07 (d, *J*=8.9, 2H, Ph), 7.72 (m, 2H, H-7, H-9), 7.09 (m, 1H, H-8), 7.0 (d, *J*=8.9, 2H, Ph), 6.84 (s, 1H, H-3), 3.87 (s, 3H, OCH_3). ^{13}C NMR ($CDCl_3$) δ = 161.7 (C-2), 161.3 (C-4), 158.4 (C-9a), 150.7 (Ph), 136.1 (C-7), 129.0 (Ph), 128.9 (Ph), 127.2 (C-6), 126.4 (C-9), 114.1 (Ph), 114.9 (C-8), 98.7 (C-3), 55.3 (OCH_3). GC/MS (EI, 70 eV): *m/z* (%) = 252 (M^+, 87), 223 (100), 78 (75), 51 (28).

2-(4-Nitrophenyl)-4*H*-pyrido[1,2-*a*]pyrimidin-4-ones (**3i**).

This compound was obtained as yellow solid, yield 55 %, Mp. 217 - 218 ºC. ^{1}H NMR ($CDCl_3$) δ = 9.01 (d, *J*=6.9, 1H, H-6), 8.22 (m, 4H, Ph), 7.74 (m, 2H, H-7, H-9), 7.15 (m, 1H, H-8), 6.87 (s, 1H, H-3). ^{13}C NMR ($CDCl_3$) δ = 157.9 (C-2), 157.6 (C-4), 150.8 (C-9a), 148.5 (Ph), 142.7 (Ph), 138.1 (C-7), 128.5 (Ph), 127.1 (C-6), 126.4 (C-9), 123.8 (Ph), 116.7 (C-8), 100.1 (C-3). GC/MS (EI, 70 eV): *m/z* (%) = 267 (M^+, 89), 239 (77), 192 (100), 78 (96), 51 (41).

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