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A Ready One-pot Preparation for 7-Oxa(or thia)-3,4,6-triazabenz[*d,e*]anthracene and 7-Oxa-3,4,6,9-tetrazabenz[*d,e*]anthracene Derivatives

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Abstract: Derivatives of 7-oxa-3,4,6-triazabenz[*d,e*]anthracene, 7-oxa-3,4,6,9-tetrazabenz[*d,e*]anthracene and 7-thia-3,4,6-triazabenz[*d,e*]anthracene are obtained from the appropriate substituted *o*-aminonitrile pyridine derivatives and *N,N*-dimethyldichloromethyleniminium chloride (phosgeniminium chloride). Copyright © 1996 Elsevier Science Ltd

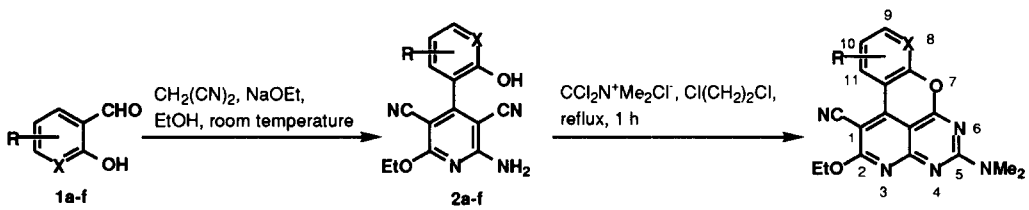
The DNA intercalating agents constitute one of the most important types of antitumor drugs. They are flat, generally aromatic or heteroaromatic polycyclic molecules with one or two flexible cationic side chains in the appropriate position bound to DNA by inserting and stacking between the base pair of the double helix.[1] The acridines, actinomycines and anthracyclines have been well characterized as intercalators of DNA and represent three types of drug molecules early and most thoroughly investigated.[2] Their biological activities are probably due to their causing of double-strand DNA break, and some of them are used clinically at present for the treatment of leukemia.[3] There is a continuous widespread interest in the synthesis of new heterocyclic rings stimulated by recent reports that a wide range of polyheterocyclic compounds isolated from marine organisms showed antitumor activity.[4] Tetracyclic compounds such as 2-dimethylamino[1]benzothiopyrano[4,3,2-*de*]quinoline,[5] 1-amino-6-methyl[1]benzothiopyrano[4,3,2-*de*]quinolin-2(3*H*)-one,[6] 10-chloro-*N,N*-dimethyl[1]benzothiopyrano[4,3,2-*de*]cinnoline-1-ethanamine,[7] pyrido[3',2':5,6]thiopyrano[4,3,2-*de*]-quinoline,[8] [1]benzopyrano[4,3,2-*de*]naphthyridine derivatives,[9] dibenzo[*b,d*]pyranones,[10] and other dibenzopyranones and benzonaphthopyranones [11] were already synthesized and reported to have promising antitumor activity or analgesic and psychopharmacological properties.

Organic cyano compounds are versatile reagents which have been extensively used in heterocyclic synthesis. An enormous number of reports on the utility of these compounds in the synthesis of heterocycles has been reported.[12] Heterocyclic β-enaminonitriles are useful synthetic intermediates for the preparation of heterocyclic systems having potential biological activity.[13] Whereas the known reactions of these synthetic intermediates with amines, cyanates, isothiocyanates, urea, carbon disulfide, chlorocarbonates, γ-oxoalcohols, etc. involve initial direct reaction of either the amino group (with the attacking oxo group) or the nitrile group

(with the attacking amino group), and this is then followed by cyclization through the alternative group, this work concerns condensations of β-enaminonitrile derivatives of aryl pyridines with phosgeniminium chloride and the reaction is quite different, involving the intramolecular ring formation from intermediates containing a reactive hydroxy or mercapto group.

The electrophilic character and structural diversity of methyleniminium salts have ensured their prominent position in synthetic chemistry.[14] Successive replacement of the methylene hydrogen atoms with chlorine leads to the chloromethylene iminium salts (Vilsmeier-Haack reagents), and finally to the dichloromethylene iminium salts first characterized by Viehe and his co-workers.[15] The chemistry of iminium salts, which can function as Vilsmeier or Mannich reagents, has proved to be very useful in synthetic chemistry, especially in various one-step heterocyclization reactions by insertion of one carbon atom bearing a dialkylamino group.[16] Dichloromethyleniminium salts possess three readily displaceable chlorine atoms and condense readily with CH-acidic compounds such as ketones, carboxylic acid and chlorides, nitriles and amides to give new electrophilic synthons (amide chlorides, α-chloroenamines, 1,3-dichlorotrimethinecyanines, etc.) which react further to produce, through either inter- or intra-molecular processes, various types of functionalized 5-, 6- and 7-membered ring systems.[16] Syntheses of fused bi- and polycyclic compounds by annelation of a pyrimidine ring to an existing ring are very numerous and were the subject of recent review.[17] In the course of our work on heterocyclic compound synthesis, we have previously reported an efficient access to polyheterocyclic compounds containing the pyrimidine ring by utilizing phosgeniminium chloride.[18] In this study, and following our long standing involvement on the synthesis and biological activity of polyheterocyclic systems which contain a pyrimidine moiety,[18,19] we report on a convenient one-pot synthesis of 7-oxa-3,4,6-triazabenz[*d,e*]anthracenes **3a-e**, 7-thia-3,4,6-triazabenz[*d,e*]anthracene **3f** and 7-oxa-3,4,6,9-tetrazabenz[d,e]anthracene **10a** involving 2-amino-3-cyanopyridines and (dichloromethylene) dimethylammonium chloride as starting materials.

Scheme 1

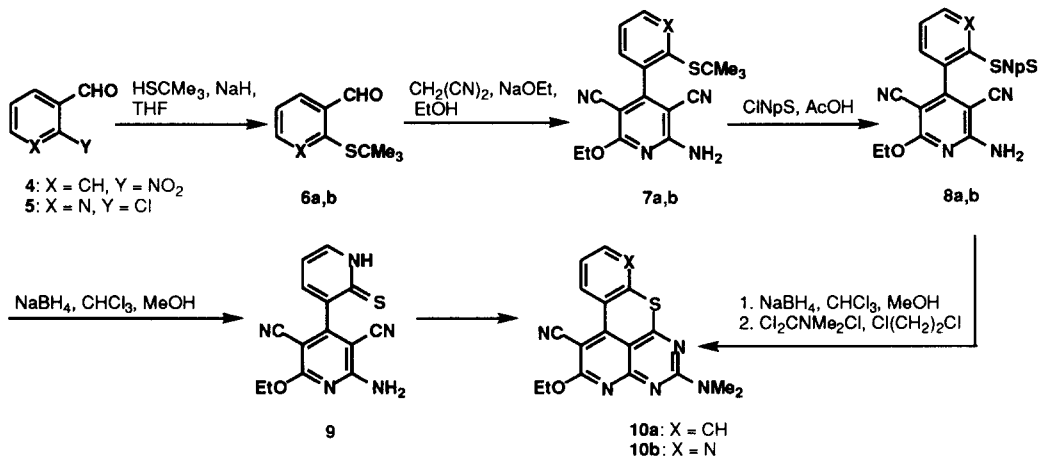


1	R	X	1	R	X
a	H	CH	**d**	3-OCH_3	CH
b	5-NO_2	CH	**e**	4-OCH_3	CH
c	5-Cl	CH	**f**	H	N

The requisite starting materials, 2-amino-3-cyano-6-ethoxy-4-(2-hydroxyphenyl)pyridine derivatives **2a-f** were prepared by condensation of *o*-hydroxybenzaldehydes **1a-f** with malononitrile according to the known procedure.[20] On treatment with *N,N*-dimethyldichloromethyleniminium chloride in refluxing 1,2,-dichloroethane, **2** underwent one-pot cyclization to the corresponding fused 7-oxa-3,4,6-triazabenz-[*d,e*]anthracenes **3a-e**. Fused tetraheterocyclic compound **3f** was synthesized from the key pyridine intermediate **2f**. The latter compound, in turn, was prepared upon treatment of *o*-hydroxynicotinaldehyde with

malononitrile in the presence of sodium ethoxide. 2-Amino-3-cyanopyridine **2f** was refluxed with phosgeniminium chloride in 1,2-dichloroethane and the expected 7-oxa-3,4,6,9-tetrazabenz[*d*,*e*]anthracene **3f** was obtained in low yield (20%). The structure of substituted benzopyranopyridopyrimidines **3** were consistent with their elemental analyses and spectral data. The NMR and IR spectra give no signal due to the hydrogen of the hydroxyl group and its mass spectra showed the expected molecular ion peak.

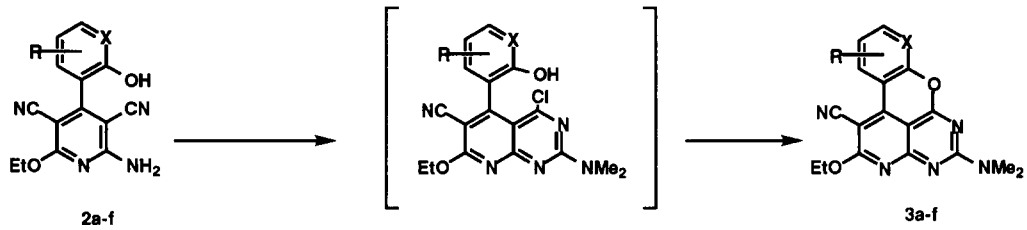
Scheme 2



o-Mercaptobenzaldehyde and other unstable cyclic or heterocyclic mercapto groups can be protected as *tert*-butylthioethers.[21] Furthermore, it was found that thiolation of cyclic and heterocyclic systems containing reactive halogen or nitro substituents can conveniently be carried out *via* the easily prepared *tert*-butylsulfides.[20] In this context, 7-thia-3,4,6-triazabenz[*d*,*e*]anthracene **10a** was synthesized as shown in Scheme 2. The readily available aldehydes **6a,b**[22] react smoothly with malononitrile to provide the pyridine derivatives **7a,b** in moderate yields. The *tert*-butyl group was removed from the thiol group by treatment with (2-nitrophenyl)sulfenyl chloride (NpSCl) to give disulfide derivatives **8a** and **8b** in 90 and 85% yields, respectively. Finally, successive reduction of the *S*-(2-nitrophenyl)sulfenyl derivative **8a** with sodium borohydride and subsequent treatment with the phosgeniminium salt caused cyclization to form the expected 7-thia-3,4,6-triazabenz[*d*,*e*]anthracene **10a** in 25% yield. The structures assigned to these compounds were unequivocally confirmed by elemental analyses, as well as IR, mass, and NMR spectral data. The data used to characterize all the compounds prepared are given in the Experimental.

Unfortunately, similar treatment of nitrophenyl sulfenyl derivative **8b** with sodium borohydride and phosgeniminium chloride resulted in an intractable mixture of products. Similarly, reaction of the thiol derivative **9**, available from the 2-nitrophenyldithio[3,4']bipyridine **8b** and sodium borohydride, with *N*,*N*-dimethyldichloromethyleniminium chloride resulted in a multi-component mixture. The mass spectrum of the crude products showed an ion peak at m/z= 350 corresponding to the molecular ion of the expected 7-thia-3,4,6,9-tetrazabenz[*d*,*e*]anthracene **10b**, but the attempts to purify the crude products were not successful.

Since phosgeniminium chloride condenses readily with nucleophiles to give amide chlorides, the reaction can be assumed to proceed as follows:



2a-f **3a-f**

As shown above, the reaction of β-aminonitrile derivatives **2a-f** and **8a** with (dichloromethylene)-dimethylammonium chlorides provides a general route to 7-oxa-3,4,6-triazabenz[*d,e*]anthracene, 7-thia-3,4,6-triazabenz[*d,e*]anthracene and 7-oxa-3,4,6,9-tetrazabenz[*d,e*]anthracene ring systems. This one-pot procedure may be useful in view of the pharmacological interest in these types of compounds.

EXPERIMENTAL PART

All reagents used were commercial grade chemicals from freshly opened containers. Melting points were determined on a Büchi 510 apparatus and are uncorrected. IR spectra were recorded as potassium bromide disks on a Perkin-Elmer 383 spectrophotometer. ^1H and ^{13}C NMR spectra were obtained on a Bruker AC 200F instrument at room temperature. Mass spectra were obtained on a VG QUATTRO spectrometer. The Silica gel 60 $HF_{254+366}$ used for analytical thin layer chromatography and the Silica gel 60 (230-400 mesh) employed for flash chromatography were purchased from Merck. Microanalyses for C, H, and N were performed by the Elemental Analyses General Service of the University of La Coruña.

Compounds **5**[23] and **6a**[22] were prepared according to the literature procedures.

2-Amino-4-aryl(or heteroaryl)-3,5-dicyano-6-ethoxypyridines (2a-f and 7a,b); General Procedure.

To a solution of sodium ethoxide (from 0.06 mole of Na) in EtOH (50 ml) was added malononitrile (0.04 mole), and then the appropriate aldehyde (0.02 mole). The solution was stirred at room temperature for 12h. The reaction mixture was poured into water (400 ml) and neutralized with 2N HCl. The resulting mixture was worked up in one of the following ways: (A) the solid formed was filtered off and recrystallized from a suitable solvent. (B) the solution was extracted with ether (150 ml), washed with brine, dried over Na_2SO_4, and then concentrated *in vacuo*. The crude product was purified by flash chromatography.

2-Amino-3,5-dicyano-6-ethoxy-4-(2-hydroxyphenyl)pyridine ***2a***. Recrystallized from EtOH/acetone. (32%); mp 201-203°C. IR (KBr, cm^{-1}): 3300 (NH); 2220 (CN); 1630; 1530; 1380. ^1H NMR δ ($CDCl_3$): 1.45 (t, 3 H, J = 7.1 Hz, CH_3); 4.48 (q, 2 H, J = 7.1 Hz, CH_2); 5.94 (br s, 1H); 7.09-7.54 (m, 4H); 9.04 (dd, 1H, J = 1.5 Hz, J = 8.3 Hz); 10.46 (br s, 1H). ^{13}C NMR δ ($CDCl_3$): 14.4 (CH_3); 63.5 (CH_2); 116.0, 117.6 (CN); 116.5; 123.8; 126.3; 133.0; 145.1; 152.0; 157.0; 160.1; 167.5. MS (EI, *m/z*, %): 280 (M^+, 100); 265 (21); 252 (42); 236 (75). Anal. Calcd. for $C_{15}H_{12}N_4O_2$: C, 64.28; H, 4.32; N, 19.99. Found C, 64.42; H, 4.21; N, 19.77.

2-Amino-3,5-dicyano-6-ethoxy-4-(2-hydroxy-5-nitrophenyl)pyridine ***2b***. Recrystallized from EtOH/acetone. (38%); mp 268-270°C. IR (KBr, cm^{-1}): 3420, 3330, 3240; 2220 (CN); 1640; 1570; 1340. ^1H NMR δ (DMSO-d_6): 1.34 (t, 3 H, J = 7.1 Hz, CH_3); 4.43 (q, 2 H, J = 7.1 Hz, CH_2); 7.15 (d, 1H, J = 8.0 Hz, H-6'); 8.00 (br s, 2H, NH_2); 8.25-8.30 (m, 2H, H-3', H-4'); 11.82 (s, 1H, OH). ^{13}C NMR δ (DMSO-d_6): 14.4 (CH_3); 63.5 (CH_2); 84.3, 84.6 (C-3, C-5); 114.9, 115.2 (CN); 116.8 (C-3'); 122.1 (C-1'); 126.3, 127.6 (C-4', C-6'); 139.4 (C-5'); 156.8; 160.8; 161.0; 165.2 (C-2, C-4, C-6, C-2'). MS (EI, *m/z*, %): 325 (M^+, 42); 297 (31); 281 (22); 269 (18); 250 (27). Anal. Calcd. for $C_{15}H_{11}N_5O_4$: C, 55.39; H, 3.41; N, 21.53. Found C, 55.58; H, 3.19; N, 21.59.

2-Amino-3,5-dicyano-6-ethoxy-4-(5-chloro-2-hydroxyphenyl)pyridine ***2c***. Recrystallized from acetone. (35%); mp 194-196°C. IR (KBr, cm^{-1}): 3440, 3260, 3120; 2220 (CN); 1640; 1600; 1380. ^1H NMR δ (DMSO-d_6): 1.33 (t, 3 H, J = 7.1 Hz, CH_3); 4.41 (q, 2 H, J = 7.1 Hz, CH_2); 6.98 (d, 1H, J = 8.6 Hz, H-6'); 7.31-7.40 (m, 2H, H-3', H-4'); 7.92 (br s, 2H, NH_2); 10.35 (s, 1H, OH). ^{13}C NMR δ (DMSO-d_6): 14.3 (CH_3); 63.5 (CH_2); 84.3, 84.5 (C-3, C-5); 114.9, 115.3 (CN); 117.8 (C-3'); 122.4, 123.1 (C-1', C-5'); 128.1, 131.0 (C-4', C-6'); 153.3 (C-2'); 157.7; 160.9; 165.1 (C-2, C-4, C-6). MS (EI, *m/z*, %): 316 (M^++2, 18); 314 (M^+, 52); 299 (13); 286 (19); 270 (84). Anal. Calcd. for $C_{15}H_{11}N_4O_2Cl$: C, 57.27; H, 3.52; N, 17.80. Found C, 57.11; H, 3.73; N, 17.66.

2-Amino-3,5-dicyano-6-ethoxy-4-(2-hydroxy-3-methoxyphenyl)pyridine ***2d***. Recrystallized from EtOH/acetone. (34%); mp 230-232°C. IR (KBr, cm^{-1}): 3390, 3320, 3140; 2220 (CN); 1630; 1600; 1380. ^1H NMR δ (DMSO-d_6): 1.35 (t, 3 H, J = 7.1 Hz, CH_3); 3.88 (s, 3H, OCH_3); 4.43 (q, 2 H, J = 7.1 Hz, CH_2); 7.20-7.35 (m, 2H); 8.38-8.45 (m, 2H); 8.86 (s, 1H, OH); 10.43 (d, 1H, J = 4.5 Hz, NH). MS (EI, *m/z*, %): 310 (M^+, 58); 295 (16); 266 (100). Anal. Calcd. for $C_{16}H_{14}N_4O_3$: C, 61.93; H, 4.55; N, 18.06. Found C, 62.09; H, 4.32; N, 18.21.

2-Amino-3,5-dicyano-6-ethoxy-4-(2-hydroxy-4-methoxyphenyl)pyridine ***2e***. Recrystallized from EtOH/acetone. (14%). IR (KBr, cm^{-1}): 3380, 3340, 3140; 2220 (CN); 1630. ^1H NMR δ (DMSO-d_6): 1.34 (t, 3 H, J = 7.1 Hz, CH_3); 3.84 (s, 3H, OCH_3); 4.40 (q, 2 H, J = 7.1 Hz, OCH_2); 6.67 (d, 1H, J = 2.3 Hz); 6.98 (dd, 1H, J = 2.3, J = 9.1 Hz); 8.33 (d, 1H, J = 3.8 Hz, NH); 8.62 (s, 1H, OH); 10.33 (d, 1H, J = 4.3 Hz, NH). MS (EI, *m/z*, %): 310 (M^+, 100); 295 (27); 282 (38); 266 (78). Anal. Calcd. for $C_{16}H_{14}N_4O_3$: C, 61.93; H, 4.55; N, 18.06. Found C, 61.72; H, 4.71; N, 18.20.

2-Amino-3,5-dicyano-6-ethoxy-4-(2-hydroxypyrid-3-yl)pyridine ***2f***. Recrystallized from dimethylformamide. (43%); mp >300 °C. IR (KBr, cm^{-1}): 3390, 3300 (NH); 2220, 2210 (CN). ^1H NMR δ (DMSO-d_6): 1.33 (t, 3 H, J = 7.1 Hz, CH_3); 4.40 (q, 2 H, J = 7.1 Hz, OCH_2); 7.57 (dd, 1H, J = 6.6, J = 1.9 Hz); 7.64 (dd, 1H, J = 6.8, J = 1.9 Hz); 7.88 (br s, 2H, NH_2); 12.14 (br s, 1H, NH). MS (EI, *m/z*, %): 281 (M^+, 100); 266 (25); 253 (62); 237 (24); 226 (51). Anal. Calcd. for $C_{14}H_{11}N_5O_2$: C, 58.78; H, 3.94; N, 24.90. Found C, 58.91; H, 4.16; N, 24.81.

2-Amino-3,5-dicyano-6-ethoxy-4-(2-tert-butylthiolphenyl)pyridine ***7a***. Purified by flash chromatography using hexane/AcOEt 4:1 v/v as eluent. (45%); mp 174-176 °C. IR (KBr, cm^{-1}): 3380, 3210 (NH); 2220 (CN); 1640; 1580. ^1H NMR δ ($CDCl_3$): 1.22 (s, 9H, $SCMe_3$); 1.42 (t, 3 H, J = 7.1 Hz, CH_3); 4.44 (q, 2 H, J =

7.1 Hz, OCH_2); 5.69 (br s, 2H, NH_2); 7.31-7.78 (m, 4H). ^{13}C NMR δ ($CDCl_3$): 14.1 (CH_3); 31.1 ($SCMe_3$); 47.8 ($SCMe_3$); 64.1 (CH_2); 85.9, 88.1 (C-3, C-5); 114.5, 115.4 (CN); 126.1, 129.3, 130.0 (C-4', C-5', C-6'); 130.6 (C-1'); 139.8 (C-3'); 142.0 (C-2'); 160.0, 161.0, 165.5 (C-2, C-4, C-6). MS (EI, *m/z*, %): 352 (M^+, 13); 296 (50); 263 (49); 252 (100); 241 (43). Anal. Calcd. for $C_{19}H_{20}N_4OS$: C, 64.75; H, 5.72; N, 15.90. Found C, 64.64; H, 5.79; N, 16.08.

2-Amino-2'-tert-butylthio-6-ethoxy[3',4]bipyridine-3,5-dicarbonitrile ***7b.*** Purified by flash chromatography using hexane/CH_2Cl_2 1:1 v/v as eluent. (37%); mp 177-179 °C. IR (KBr, cm^{-1}): 3420, 3310 (NH); 2220 (CN). ^1H NMR δ ($CDCl_3$): 1.45 (t, 3 H, J = 7.1 Hz, CH_3); 1.60 (S, 9H, $SCMe_3$); 4.48 (q, 2 H, J = 7.1 Hz, OCH_2); 5.59 (br s, 2H, NH_2); 7.14 (dd, 1H, J = 7.8 Hz, J = 4.9 Hz, H-5'); 7.38 (dd, 1H, J = 7.8 Hz, J = 1.9 Hz, H-6'); 8.59 (dd, 1H, J = 4.8 Hz, J = 1.7 Hz, H-4'). ^{13}C NMR δ ($CDCl_3$): 11.7 (CH_3); 28.3 ($SCMe_3$); 46.9 ($SCMe_3$); 61.8 (CH_2); 82.4, 84.9 (C-3, C-5); 111.4, 112.3 (CN); 116.9 (C-5'); 127.3 (C-1'); 133.3 (C-6'); 147.9 (C-4'); 155.2, 158.1, 163.4 (C-2, C-4, C-6). MS (EI, *m/z*, %): 353 (M^+, 5); 297 (87); 271 (88). Anal. Calcd. for $C_{18}H_{19}N_5OS$: C, 61.17; H, 5.42; N, 19.82. Found C, 61.02; H, 5.53; N, 19.77.

1-Cyano-5-dimethylamino-2-ethoxy-7-oxa-3,4,6-triazabenz[d,e]anthracenes 3a-e and 1-cyano-5-dimethylamino-2-ethoxy-7-oxa-3,4,6,8-tetrazabenz[d,e]anthracene 3f; General Procedure.

A solution of **2** (5.4 mmol) and phosgeniminium chloride (10.8 mmol) in 1,2-dichloroethane (15 mL) was refluxed for 30 min. The solid formed was filtered off and recrystallized from dimethylformamide.

1-Cyano-5-dimethylamino-2-ethoxy-7-oxa-3,4,6-triazabenz[d,e]anthracene ***3a.*** (78%); mp 298-300°C. IR (KBr, cm^{-1}): 2220 (CN), 1630; 1540; 1310. ^1H NMR δ (C_5D_5N): 1.32 (t, 3H, J = 7.2 Hz, CH_3); 3.20 (s, 3H, NMe_2); 3.23 (s, 3H, NMe_2); 4.61 (q, 2H, J = 7.1 Hz, OCH_2); 7.31 (t, 1H, J = 8.0 Hz); 7.44 (d, 1H, J = 8.1 Hz); 7.56-7.62 (m, 1H); 9.25 (d, 1H, J = 8.0 Hz). MS (EI, m/z, %): 333 (M^+, 100); 318 (59); 308 (48); 290 (98). Anal. Calcd. for $C_{18}H_{15}N_5O_2$: C, 64.86; H, 4.54; N, 21.01. Found C, 64.95; H, 4.63; N, 21.09.

1-Cyano-5-dimethylamino-2-ethoxy-10-nitro-7-oxa-3,4,6-triazabenz[d,e]anthracene ***3b.*** (15%); mp >300°C. IR (KBr, cm^{-1}): 2220 (CN), 1640; 1610; 1530; 1330. ^1H NMR δ (C_5D_5N): 1.31 (t, 3H, J = 7.2 Hz, CH_3); 3.22 (s, 3H, NMe_2); 3.25 (s, 3H, NMe_2); 4.60 (q, 2H, J = 7.1 Hz, OCH_2); 7.66 (d, 1H, J = 9.2 Hz, H-8); 8.53 (dd, 1H, J = 9.1 Hz, J = 2.6 Hz, H-9); 10.18 (d, 1H, J = 2.6 Hz, H-11). MS (EI, m/z, %): 378 (M^+, 56); 363 (26); 349 (25); 335 (39); 321 (37); 289 (36). Anal. Calcd. for $C_{18}H_{14}N_6O_4$: C, 57.14; H, 3.73; N, 22.21. Found C, 57.01; H, 3.90; N, 22.03.

10-Chloro-1-cyano-5-dimethylamino-2-ethoxy-7-oxa-3,4,6-triazabenz[d,e]anthracene ***3c.*** (77%); mp >300°C. IR (KBr, cm^{-1}): 2210 (CN), 1630; 1540; 1400. ^1H NMR δ (C_5D_5N): 1.31 (t, 3H, J = 7.2 Hz, CH_3); 3.20 (s, 3H, NMe_2); 3.24 (s, 3H, NMe_2); 4.59 (q, 2H, J = 7.1 Hz, OCH_2); 7.45 (d, 1H, J = 8.9 Hz, H-8); 7.65 (dd, 1H, J = 8.9 Hz, J = 2.4 Hz, H-9); 9.24 (d, 1H, J = 2.4 Hz, H-11). MS (EI, m/z, %): 369 (M^++2, 33); 367 (M^+, 100); 352 (52); 338 (48); 324 (86); 310 (52). Anal. Calcd. for $C_{18}H_{14}N_5O_2Cl$: C, 58.78; H, 3.84; N, 19.04. Found C, 59.02; H, 3.71; N, 19.21.

1-Cyano-5-dimethylamino-2-ethoxy-8-methoxy-7-oxa-3,4,6-triazabenz[d,e]anthracene ***3d.*** (60%); mp >300°C. IR (KBr, cm^{-1}): 2210 (CN), 1630; 1550; 1310; 1270. ^1H NMR δ (C_5D_5N): 1.31 (t, 3H, J = 7.2 Hz, CH_3); 3.16 (s, 3H, NMe_2); 3.21 (s, 3H, NMe_2); 3.83 (s, 3H, OCH_3); 4.60 (q, 2H, J = 7.1 Hz, OCH_2); 7.17-7.27 (m, 2H); 8.85 (dd, 1H, J = 7.3 Hz, J = 2.3 Hz, H-9). MS (EI, m/z, %): 363 (M^+, 97); 348 (64); 334 (54); 320 (100); 306 (62); 292 (39). Anal. Calcd. for $C_{19}H_{17}N_5O_3$: C, 62.80; H, 4.72; N, 19.27. Found C, 63.03; H, 4.67; N, 19.41.

1-Cyano-5-dimethylamino-2-ethoxy-9-methoxy-7-oxa-3,4,6-triazabenz[d,e]anthracene ***3e.*** (68%); mp 283-284°C. IR (KBr, cm^{-1}): 2210 (CN), 1640; 1610; 1590; 1540; 1320. ^1H NMR δ (C_5D_5N): 1.32 (t, 3H, J = 7.1 Hz, CH_3); 3.21 (s, 3H, NMe_2); 3.24 (s, 3H, NMe_2); 3.77 (s, 3H, OCH_3); 4.61 (q, 2H, J = 7.1 Hz, OCH_2); 6.94 (dd, 1H, J = 9.1 Hz, J = 2.7 Hz, H-10); 7.03 (d, 1H, J = 2.5 Hz, H-8); 9.15 (d, 1H, J = 9.1 Hz, H-11). MS (EI, m/z, %): 363 (M^+, 63); 348 (49); 334 (31); 320 (68); 306 (39). Anal. Calcd. for $C_{19}H_{17}N_5O_3$: C, 62.80; H, 4.72; N, 19.27. Found C, 62.97; H, 4.95; N, 19.07.

1-Cyano-5-dimethylamino-2-ethoxy-7-oxa-3,4,6,8-tetrazabenz[d,e]anthracene ***3f.*** (20%); mp >300°C. IR (KBr, cm^{-1}): 2230 (CN), 1640. ^1H NMR δ ($CDCl_3$): 1.52 (t, 3H, J = 7.1 Hz, CH_3); 3.35 (s, 3H, NMe_2); 3.39 (s, 3H, NMe_2); 4.68 (q, 2H, J = 7.1 Hz, OCH_2); 7.47 (dd, 1H, J = 8.1 Hz, J = 4.7 Hz, H-10); 8.65 (dd, 1H, J = 4.6 Hz, J = 1.9 Hz, H-11); 9.47 (dd, 1H, J = 8.1 Hz, J = 1.8 Hz, H-9). MS (EI, m/z, %): 334 (M^+, 100); 319 (49); 305 (49); 291 (87); 277 (58). Anal. Calcd. for $C_{17}H_{14}N_6O_2$: C, 61.07; H, 4.22; N, 25.14. Found C, 61.21; H, 4.11; N, 25.23.

2-tert-Butylthiopyridine-3-carbaldehyde (6b)

To an ice-cooled suspension of sodium hydride (0.47 g, 20 mmol) in dry THF (40 ml), 2-methyl-2-propanethiol (1.40 g, 15 mmol) was slowly added. The resulting white suspension was heated to room temperature and stirred for 1h. The reaction mixture was ice-cooled again and **6** (2.0 g, 14 mmol) was slowly added. The mixture was heated to room temperature and stirred at this temperature for 30 min. The reaction mixture was then poured onto ice-cooled water (100 ml). The aqueous solution was extracted with AcOEt (3x50 ml) and dried over Na_2SO_4. Evaporation of solvent gave an oil which was purified by flash chromatography. Elution with CH_2Cl_2:hexane (5:4 v/v) afforded **6** (1.4 g, 51%). IR (film, cm^{-1}): 2980; 2920; 1700 (CO). ^1H NMR δ ($CDCl_3$): 1.58 (s, 9H, $SCMe_3$); 7.16 (dd, 1H, J = 7.8 Hz, J = 1.8 Hz, H-4); 8.01 (dd, 1H, J = 7.8, Hz, J = 1.8 Hz, H-4); 8.61 (dd, 1H, J = 4.7, Hz, J = 1.8 Hz, H-6); 10.40 (s, 1H, CHO). MS (EI, m/z, %): 195 (M^+, 6); 139 (51); 111 (97); 84 (100). Anal. Calcd. for $C_{10}H_{13}NOS$: C, 61.51; H, 6.71; N, 7.17. Found C, 61.60; H, 6.58; N, 7.31.

Preparation of S-(2-nitrophenyl)sulfenyl derivatives (8a,b); General Procedure.

A solution of *S-tert*-butyl derivative **7** (0.30 mmol) and nitrobenzenesulfenyl chloride (0.066 g, 0.35 mmol) in acetic acid (3 ml) was stirred at room temperature for 3h. The solid formed was filtered off and recrystallized from EtOH.

2-Amino-3,5-dicyano-6-ethoxy-4-(2-nitrophenyldithio)pyridine ***8a.*** Recrystallized from EtOH. (90%); mp 203-205°C. IR (KBr, cm^{-1}): 3480, 3420 (NH); 2220 (CN); 1640; 1560. ^1H NMR δ ($CDCl_3$): 1.47 (t, 3 H, J = 7.1 Hz, CH_3); 4.50 (q, 2 H, J = 7.1 Hz, OCH_2); 5.70 (br s, 2H, NH_2); 7.22-7.77 (m, 6H); 8.04 (d, 1H, J

= 8.2 Hz); 8.27 (d, 1H, J = 8.2 Hz). ^{13}C NMR δ ($CDCl_3$): 14.2 (CH_3); 64.5 (CH_2); 85.2, 88.0 (C-3, C-5); 113.9, 114.8 (CN); 126.0, 126.7, 127.7, 127.9, 129.1, 130.6, 131.2, 133.1, 133.2, 134.7, 136.0, 145.5 (C_{arom}); 158.7, 160.5, 166.0 (C-2, C-4, C-6). MS (EI, *m/z*, %): 449 (M^+, 10); 295 (27); 269 (39); 197 (100). Anal. Calcd. for $C_{21}H_{15}N_5O_3S_2$: C, 56.11; H, 3.36; N, 15.58. Found C, 56.04; H, 3.49; N, 15.65.

2-Amino-3,5-dicyano-6-ethoxy-2'-(2-nitrophenyldithio)[3',4]bipyridine ***8b*** (85%); mp 207-209°C. IR (KBr, cm^{-1}): 3440, 3290 (NH); 2220, 2210 (CN); 1630. ^{1}H NMR δ ($CDCl_3$): 1.47 (t, 3 H, J = 7.1 Hz, CH_3); 4.50 (q, 2 H, J = 7.1 Hz, OCH_2); 5.79 (br s, 2H, NH_2); 7.29-7.64 (m, 4H); 8.02 (dd, 1H, J = 8.2 Hz, J = 1.0 Hz); 8.26 (dd, 1H, J = 8.3 Hz, J = 1.3 Hz); 8.58 (dd, 1H, J = 4.8 Hz, J = 1.5 Hz). ^{13}C NMR δ ($CDCl_3$): 14.2 (CH_3); 64.7 (CH_2); 84.7, 87.5 (C-3, C-5); 113.8, 114.6 (CN); 121.8, 125.7, 126.7, 128.3, 129.0, 134.5, 136.8, 136.9, 145.6, 151.7, 153.3, 156.2, 160.7, 166.1. MS (EI, *m/z*, %): 450 (M^+, 16); 404 (90); 372 (24). Anal. Calcd. for $C_{20}H_{14}N_6O_3S_2$: C, 53.32; H, 3.13; N, 18.66. Found C, 53.18; H, 3.25; N, 18.51.

2-Amino-3,5-dicyano-6-ethoxy-2'-thioxo-1,2-dihydro[3',4]bipyridine (9)

To a solution of **8b** (0.20 g, 0.44 mmol) in $CHCl_3$ (3 ml) was added MeOH (0.5 ml), and the solution was reduced with $NaBH_4$ (0.07 g, 1.85 mmol). After 1h the solvents were evaporated at reduced pressure. Water (5 ml) was added and the solid formed was filtered off and recrytallized from EtOH to yield **9** (0.10 g, 76%); mp 254-256°C. IR (KBr, cm^{-1}): 3400, 3300, 3200 (NH); 2220, 2210 (CN), 1640. ^{1}H NMR δ (DMSO-d_6): 1.33 (t, 3 H, J = 7.1 Hz, CH_3); 4.41 (q, 2 H, J = 7.1 Hz, OCH_2); 6.92 (t, 1H, J = 6.7 Hz, H-5'); 7.63 (dd, 1H, J = 7.2 Hz, J = 1.6 Hz, H-6'); 7.84 (dd, 1H, J = 6.3 Hz, J = 1.7 Hz, H-3'); 7.90 (s, 1H, exchangeable with D_2O). ^{13}C NMR δ (DMSO-d_6): 14.3 (CH_3); 63.4 (CH_2); 84.0, 84.3 (C-3, C-5); 112.5 (C-5'); 114.6, 115.0 (CN); 137.3 (C-3'); 137.8, 139.8 (C-4', C-6'); 159.8, 160.9, 165.2 (C-2, C-4, C-6); 175.2 (CS). MS (EI, *m/z*, %): 297 (M^+, 100); 271 (68), 243 (89). Anal. Calcd. for $C_{14}H_{11}N_5OS$: C, 56.55; H, 3.73; N, 23.55. Found C, 56.39; H, 3.87; N, 23.64.

1-Cyano-5-dimethylamino-2-ethoxy-9-methoxy-7-thia-3,4,6-triazabenz[d,e]anthracene 10a

To a solution of **8a** (0.10 g, 0.22 mmol) in $CHCl_3$ (3 ml) was added MeOH (0.5 ml), and the solution was reduced with $NaBH_4$ (0.08 g, 1.38 mmol). After 2.5h the solution was washed with H_2O, 2N HCl, and again H_2O, dried over Na_2SO_4, and evaporated. The residue (0.05g, 0.17 mmol) was dissolved in 1,2-dichloroethane (4 ml) and phosgeniminium chloride (0.05 g, 0.34 mmol) was added. The solution was heated at reflux for 30 min. The solid formed was filtered to yield **10a** (0.02 g, 25%). IR (KBr, cm^{-1}): 2210 (CN), 1580; 1400. ^{1}H NMR δ ($CDCl_3$): 1.53 (t, 3H, J = 7.1 Hz, CH_3); 3.37 (s, 6H, NMe_2); 4.73 (q, 2H, J = 7.1 Hz, OCH_2); 7.40-7.64 (M, 3H); 9.26-9.31 (m, 1H). ^{13}C NMR δ ($CDCl_3$): 14.4 (CH_3); 38.1 (NMe_2); 65.1 (CH_2); 85.8 (C-1); 104.8 (C-6b); 116.9 (CN); 124.7; 127.1; 127.7; 129.2; 132.0; 133.5; 146.8; 158.4; 159.3, 168.5, 168.8. MS (FAB, m/z, %): 350 [$(MH)^+$, 86)]. Anal. Calcd. for $C_{18}H_{15}N_5OS$: C, 61.88; H, 4.33; N, 20.04. Found C, 62.02; H, 4.23; N, 19.87.

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