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SYNTHESIS OF *E*/*Z* 3-(1*H*-BENZOTRIAZOL-1-YL)-3-(PYRIDIN-4-YL)ACRYLONITRILES AND *E*/*Z* 2-(3-IMINO-2-BENZOFURAN-1(3*H*)-YLIDENE)ACETONITRILES. AN UNUSUAL CASE OF DISPLACEMENT OF THE BENZOTRIAZOLE RING

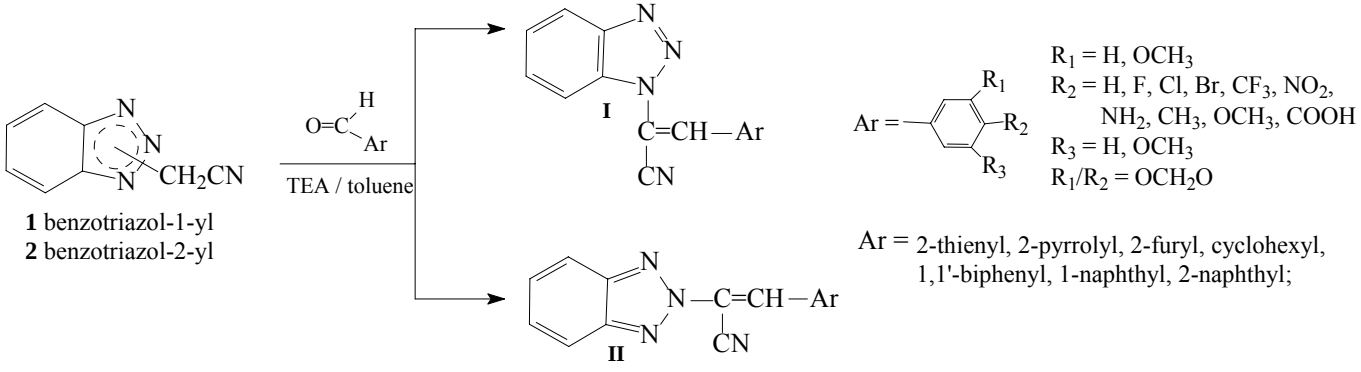
Antonio Carta,[a] Paolo Sanna,*[a] and Alessia Bacchi[b]

[a]Department of Medicinal and Toxicological Chemistry, University of Sassari, Via Muroni 23, 07100 Sassari, Italy

[b]Department of General Chemistry, University of Parma, Parco Area delle Scienze, 17AI-43100 Parma, Italy

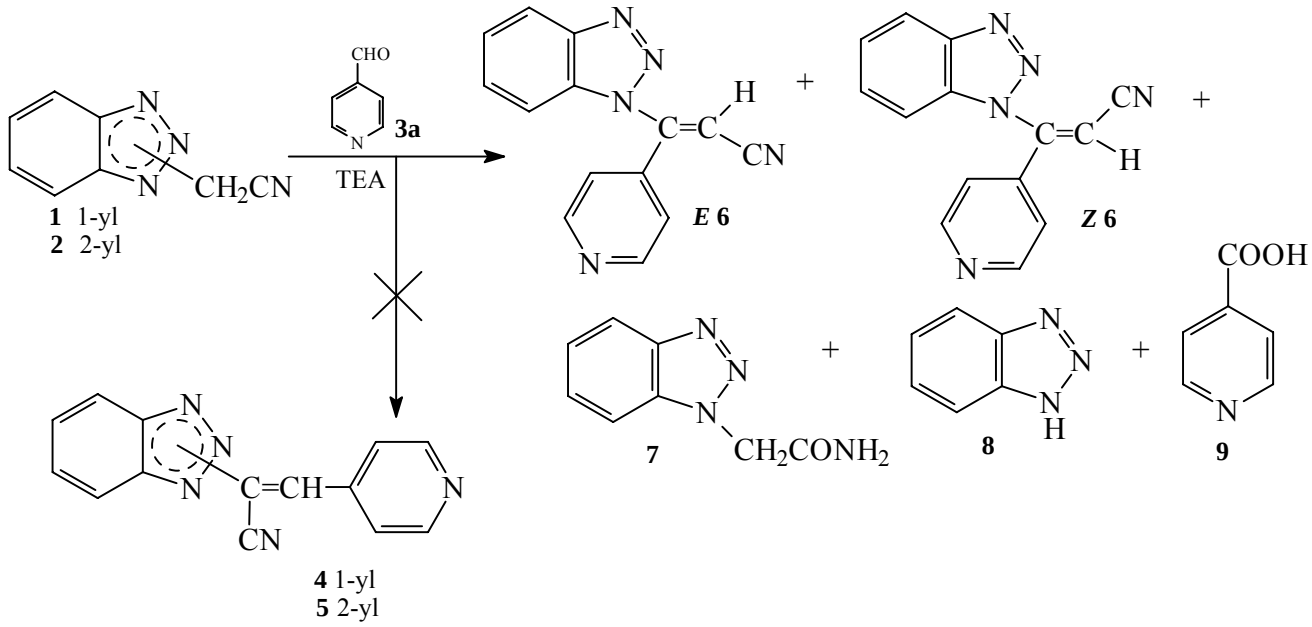
Abstract – Synthesis of 3-(1*H*-benzotriazol-1-yl)-3-(pyridin-4-yl)acrylonitriles (***E*/*Z* 6**) and 2-(3-imino-2-benzofuran-1(3*H*)-ylidene)acetonitriles (***E*/*Z* 20**), by an unusual case of displacement of the benzotriazole ring, has been described. The X-Ray structure analysis of ***Z* 20** and antimycobacterial activity of both ***E*/*Z* 6** and ***E*/*Z* 20** were also reported.

Knoevenagel condensation was extensively used for the preparation of a series of benzotriazol-1(2)-yl-acrylonitriles recently described by us as novel antimycobacterial agents.[1,2] These compounds were obtained starting from 2-(1*H*(2*H*)-benzotriazol-1(2)-yl)acetonitriles (**1** and **2**) and various arylaldehydes in refluxing toluene and in the presence of triethylamine (TEA) as catalyst. This reaction proceeded smooth and gave fair yields of both 1- and 2- substituted benzotriazoles and their *E*/*Z* isomers of general formula **I** and **II** (Scheme 1).



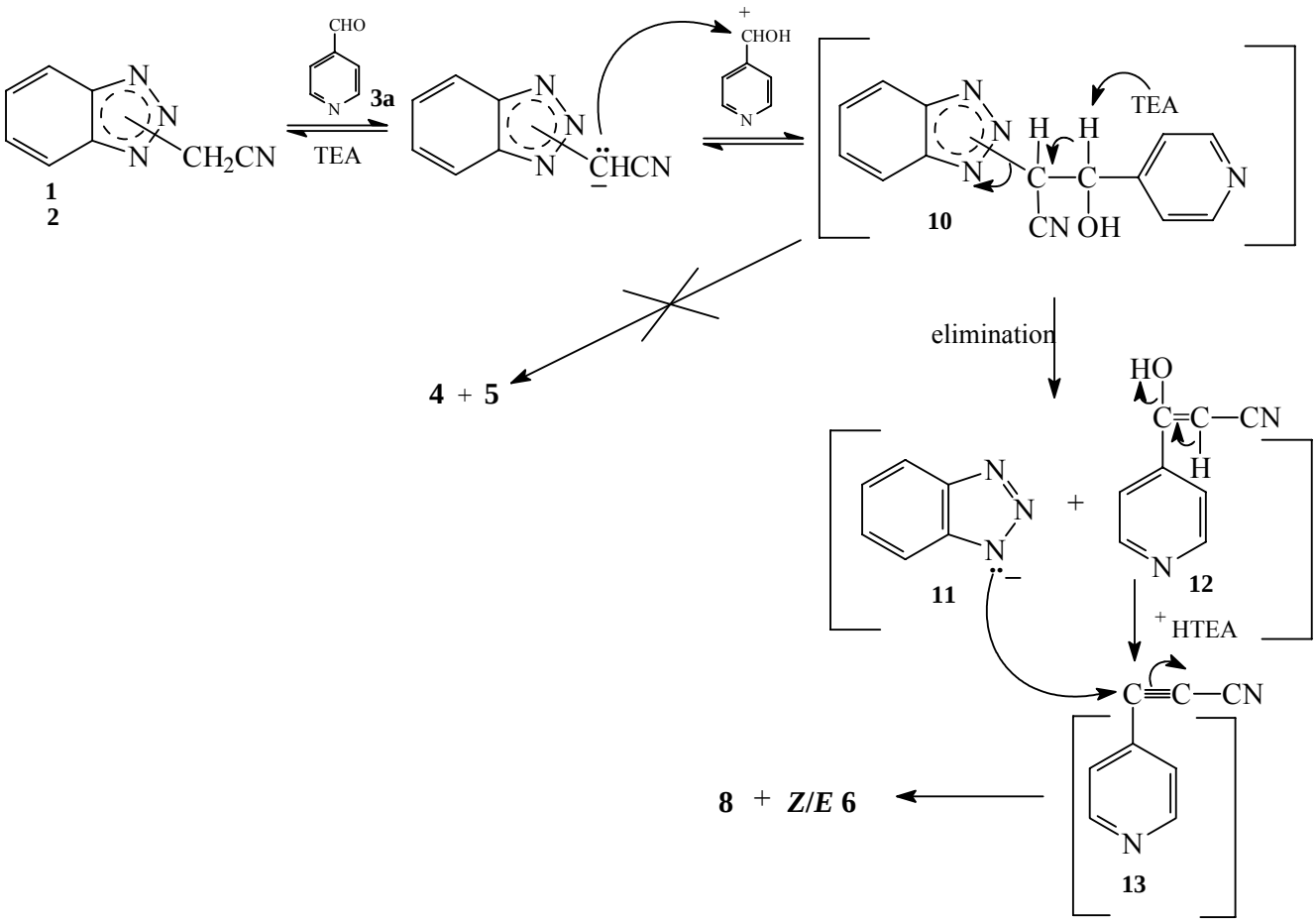
Scheme 1

In this context we planned to prepare similar compounds replacing the used aryl moiety on the acrylonitrile side chain with a 2- or 4-pyridyl ring in order to expande the structure-activity relationships. Thus, we reacted the 2-(1*H*(2*H*)-benzotriazol-1(2)-yl)acetonitriles (**1** and **2**) with 4-pyridinecarboxaldehyde (**3a**) under the same conditions with the aim to obtain the expected compounds *E*/*Z* (**4**) and *E*/*Z* (**5**). Surprisingly this reaction followed a different course and from the work up of the reaction mixture we were able to isolate identical amounts of the compounds *E* (**6**) (14%) and *Z* (**6**) (14%), the benzotriazol-1-ylacetamide (**7**) (18%), benzotriazole (**8**) (39%) and isonicotinic acid (**9**) (24%) (Scheme 2).



Scheme 2

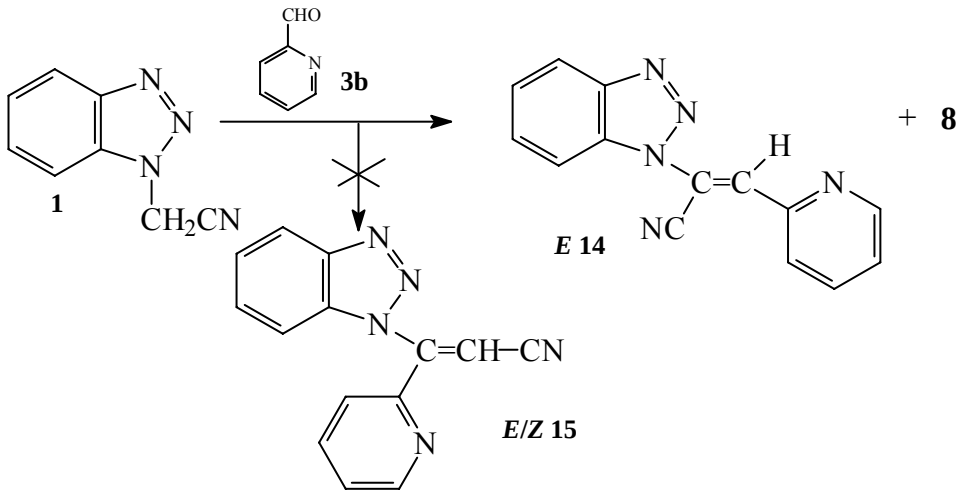
These results were very intriguing since we could observe a displacement of the benzotriazole ring taking place during the Knoevenagel reaction and it is interesting to note that starting from both **1** and **2** the only isolated compounds were the benzotriazol-1-yl derivatives (*E*/*Z* **6**), while no formation of 2-substituted isomers, as in the previous reported cases,[1,2] was observed. The obtained compounds (**6**) seem rather to come according to a Michael type addition of benzotriazole upon an activated triple bond forming during the reaction, whereas the amide (**7**) and the isonicotinic acid (**9**) are clearly products of hydrolysis of the starting reactants. We rationalised the unexpected isolation of compounds (*E*/*Z* **6**) *via* the deprotonation, under basic conditions, of the intermediate (**10**). The latter could undergo displacement of benzotriazole anion (**11**) giving the enol (**12**) which suffers water elimination to give 3-(pyridin-4-yl)prop-2-ynenitrile (**13**). The formation of *E*/*Z* (**6**) might arise from Michael addition of **11** on **13** (Scheme 3).



Scheme 3

This mechanism seems to be in good accordance with the observed behavior of the benzotriazole acting as good leaving group reported by Katritzky[3-5]and by us in the reaction of the 5-substituted benzotriazoles with diethyl ethoxymethylenemalonate (EMME) which led to the formation of either *E*/*Z* ethyl 5(6)-substituted [benzotriazol-1(2)-yl]acrylates and $N_{1,2,3}$-ethyl-5-substituted benzotriazoles.[6]

However, in order to evaluate if this behavior was dependent on the type of aldehyde or by the reaction conditions used, we repeated the same reaction either employing the pyridine-2-carboxaldehyde (**3b**) or varying the temperature of reaction. From our experiments it is easy to observe that the reaction of **1** with **3b** at the temperature of reflux gave a complex reaction mixture from which only products of degradation were detected, while operating at room temperature a normal Knoevenagel reaction took place yielding *E* **14** in 12% yield and benzotriazole (**8**), and in no way compounds (*E*/*Z* **15**) were detected (Scheme 4).



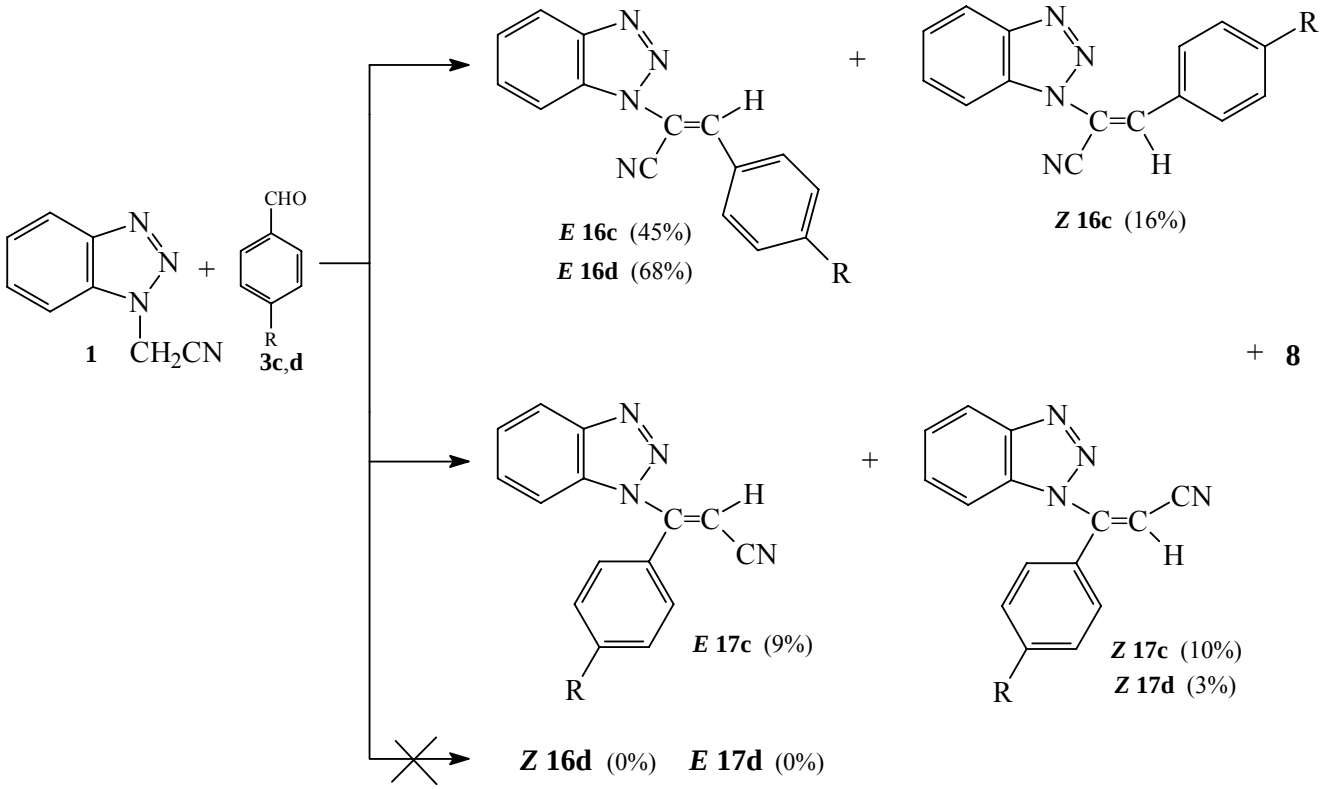
Scheme 4

At this stage to exclude that the temperature might have influenced the reaction of **1** with **3a** we repeated the same reaction at room temperature but the results were identical, although the isomer (*E* **6**) was obtained in lesser yield (2.2%) than *Z* **6** (18%).

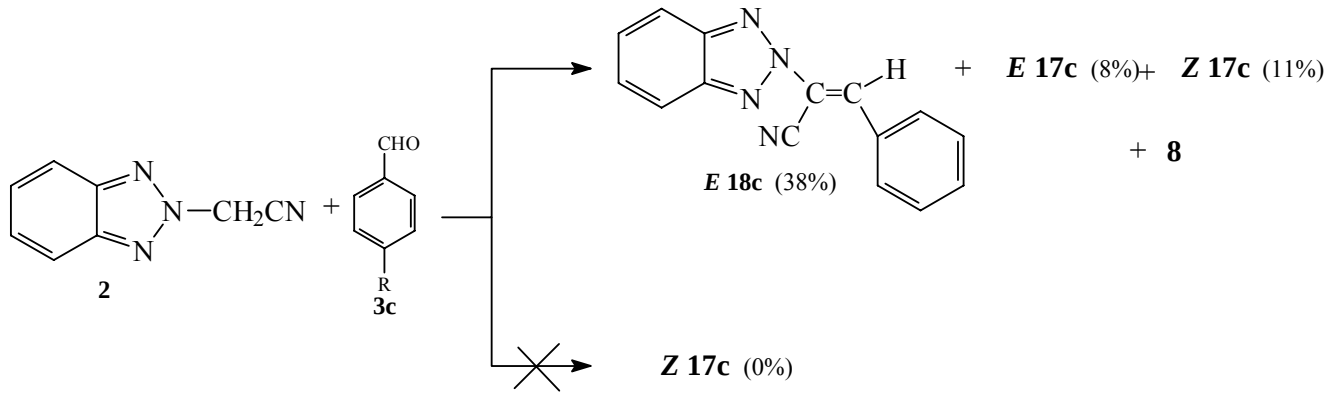
In the light of these results we have carefully re-examined all the reactions previously described. From this investigation it emerged that the previous reported reactions of **1** and **2** with the 4-nitrobenzaldehyde (**3c**) and **1** with 4-trifluoromethylbenzaldehyde (**3d**)[1] were not fully analysed and had to be re-examined since these arylaldehydes bearing a *para*-electronwithdrawing group can be compared with the 4-pyridinecarboxaldehyde.

On these grounds we were able to re-formulate those findings with the following as they are represented in Scheme 5. The reaction of **1** with **3c** afforded a mixture of compounds (*E*/*Z* **16c**), already characterised,[1] togheter with *E*/*Z* **17c** which were isolated and unambigously identified. In similar manner, the reaction of **2** with **3c** gave *E* **17c** and *Z* **17c** (previously reported as *Z* **18c**) besides the known *E* **18c**.[1] Furthermore from the reaction of **1** with **3d** the compounds (*E* **16d**) and (*Z* **17d**, previously reported as *Z* **16d**)[1] have also identified.

From the results of Schemes 2-5 we can put forward some conclusions. Arylaldehydes bearing an electronwithdrawing group in *para* position can promote displacement of benzotriazole anion in the first step of Knoevenagel condensation to give *E*/*Z* 3-(benzotriazol-1-yl)acrylonitriles as well as 2-(benzotriazol-1(2)-yl)acrylonitriles as previously reported.[1,2] The stability of the final products was very high, the only exception being recorded for the case of *E* **17c**. This compound as a solid or in organic (DMSO, chloroform, acetone, ethanol) solution was converted into a mixture of *E*/*Z* **17c** in 60:40 ratio after 25-30 days on standing (MS and ^{1}H-NMR spectral evidence).



c) R = NO_2
d) R = CF_3

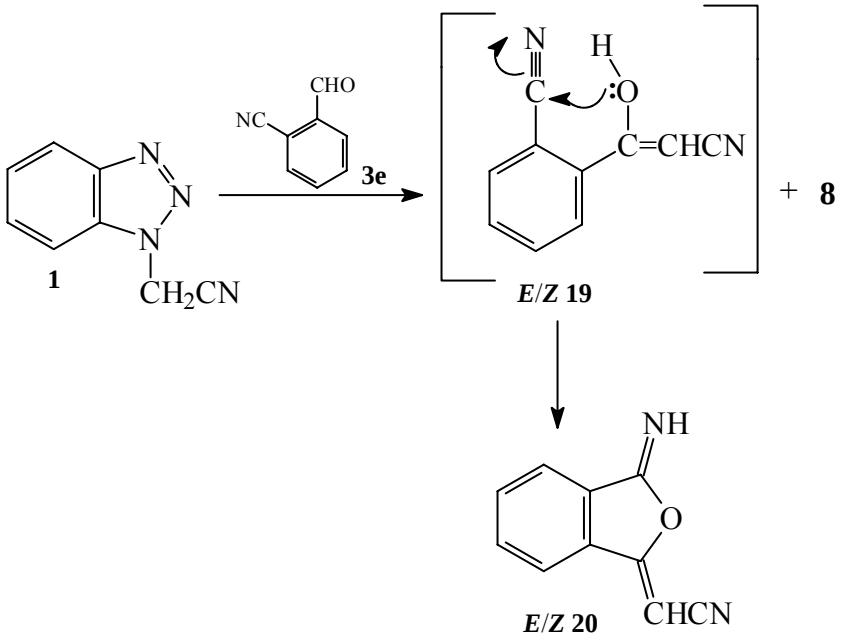


Scheme 5

The structures of the single *E*/*Z* isomers were assigned on the basis of their UV, IR, ^{1}H- and ^{13}C-NMR, and MS spectra. In particular, the chemical shift of the side chain carbon linked to benzotriazole in position 1 for the *E*/*Z* 3-(benzotriazol-1-yl)acrylonitriles (**17c**,**d**) (*C*-CN) is located in the range between 149 and 150 ppm, while the same atom in the *E*/*Z* 2-(benzotriazol-1-yl)acrylonitriles (**16c**,**d**) is located between 103 and 137 ppm. In addition, the vinylic-H in *E*/*Z* 2-(benzotriazol-1(2)-yl) derivatives exhibited a down-field shift (8.83-7.60 ppm)[1] compared with that of the *E*/*Z* 3-benzotriazolyl derivatives (**17c**,**d**)

(6.42-6.03 ppm). Analogously the corresponding carbon atoms (*HC*=C) exhibited a chemical shift in the range 135-140 ppm and 92-95 ppm respectively. From the above type of observations the assignment of the structure for isomers *E*/*Z* (**6**) came straightforward from comparison of their spectral behavior. A method of identification for the correct geometric structure of *E*/*Z* 2-(benzotriazol-1(2)-yl)acrylonitriles was previously reported;[1] in the case of *E*/*Z* 3-(benzotriazol-1-yl)acrylonitriles the vinylic-H of *E* isomers resonates more down-field (6.42 ppm) than the corresponding *Z* isomers (6.14-6.03 ppm) in accordance with our previous observations for similar compounds.[7] This behavior can be explained because of the higher diamagnetic shift of the vinylic-H, due to benzotriazole, in the *Z* isomers rather than in the *E* isomers.

Another particular reaction was observed in the case of **1** with 2-cyanobenzaldehyde (**3e**). This reaction was investigated in order to discover if the presence of a concomitant CN group in the second step of the mechanism put forward in Scheme 3 could prevent the water elimination before producing prop-2-ynenitrile. In fact the nature of the compounds isolated (*E*/*Z* **20**) (Scheme 6) and elucidation of its structure by spectroscopic experiments and X-Ray analysis (Figure 1) would confirm that at this step a competitive intramolecular nucleophilic attack by the hydroxy group was occuring to produce a mixture of isomeric 2-(3-imino-2-benzofuran-1(3*H*)-ylidene)acetonitriles (**20**) in 57% yield. This result is an interesting because it represents the first case, to our knowledge, of synthesis of isobenzofuran derivatives of phtalic anhydride type which can offer novel routes to form new organic compounds.



Scheme 6

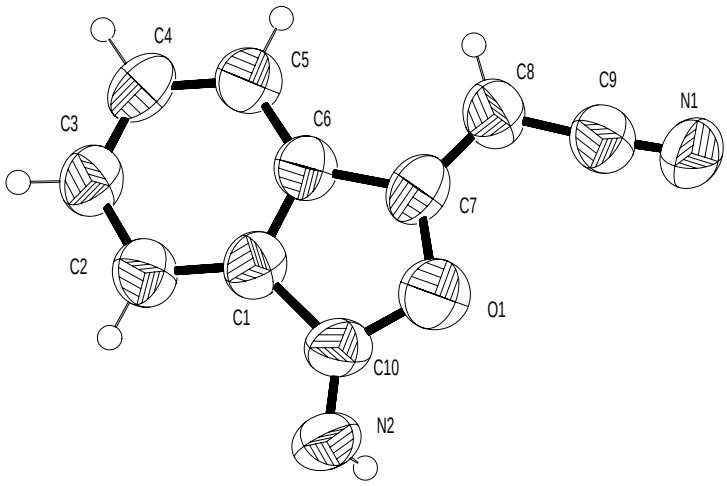


Figure 1. Perspective view of the molecular structure of ***Z* 20** as determined by X-Ray diffraction analysis. Thermal ellipsoids are drawn at the 50% probability level.

MICROBIOLOGICAL ASSAYS

Compounds (***E* 6**, ***Z* 6** and ***Z* 17c**) were submitted to Southern Research Institute, in agreement with the Tuberculosis Antimicrobial Acquisition & Coordinating Facility (TAACF) program, for to a preliminary in vitro assay of antimycobacterial activity in order to evaluate if this type of *E*/*Z* 3-(benzotriazol-1-yl)acrylonitriles were more active than those of the previous series of *E*/*Z* 2-(benzotriazol-1(2)-yl)acrylonitriles. This primary screening was conducted at 12.5 μg/mL against *M. tuberculosis* H37Rv (ATCC 2794), in BACTEC 12B medium using a broth microdilution assay.[8] The data provided by Southern Research Institute showed that compounds (***E* 6**, ***Z* 6** and ***Z* 17c**) exhibited growth inhibition (GI) of 26%, 34% and 31% respectively, while the similar 2-benzotriazolyl substituted (***E* 16c**, ***Z* 16c**, ***E* 18c** and ***E* 16d**), previously tested,[1] exhibited growth inhibition of 43%, 49%, 67% and 82% respectively. These results seem to put in evidence that for the antitubercular activity the 2-benzotriazolyl substituted acrylonitriles are more actives than those 3 substituted. In the same test compounds (***E* 20** and ***Z* 20**) resulted completely inactive.

EXPERIMENTAL

Melting points are uncorrected and were taken in open capillaries in a Digital Electrothermal IA9100 melting point apparatus. In brackets are reported the recrystallization solvents. IR spectra were recorded as nujol mulls or film on a Perkin Elmer 781 spectrophotometer and are expressed in cm^{-1}. UV spectra

are qualitative and were recorded in nm for ethanol solution with a Perkin-Elmer Lambda 5 spectrophotometer. ^{1}H-NMR spectra were recorded at 200 MHz using a Varian XL-200 spectrometer, ^{13}C-NMR spectra were recorded on the same instrument at 50 MHz. Chemical shifts are reported in ppm (δ) relative to tetramethylsilane as internal standard. MS spectra were performed on a combined HP 5790 (GC)-HP 5970 (MS) apparatus. Crystal data were measured on a Enraf-Nonius CAD4 diffractometer equipped with graphite monochromated CuKα radiation. Column chromatography was performed using 70-230 mesh (Merck silica gel 60). The progress of the reactions and the purity of the final compounds were monitored by TLC using Merck F-254 commercial plates. Light petroleum refers to the fraction with bp 40-60°C. Elemental analyses were performed at the Laboratorio di Microanalisi, Dipartimento di Scienze Farmaceutiche, University of Padua-Italy.

General procedure for the preparation of *E*/*Z* 3-(1*H*-benzotriazol-1-yl)-3-(pyridin-4-yl)acrylonitriles (*E*/*Z* 6) and *E*/*Z* 2-(3-imino-2-benzofuran-1(3*H*)-ylidene)acetonitriles (*E*/*Z* 20). To a mixture of **1** or **2** (2.0 g, 12.6 mmol) and an excess of triethylamine (3.85 g, 38 mmol) in toluene (25 mL) stirred at rt for 20 min, a solution of the appropriate arylaldehyde (**3a**) (1.66 g, 12.6 mmol) or **3e** (1.35 g, 12.6 mmol) in toluene (10 mL) was slowly added. The reaction mixture was then heated under reflux for 24 h. After removal of the solvent *in vacuo*, the crude solid residue was purified according to the indications described below.

***E*/*Z* 3-(1*H*-Benzotriazol-1-yl)-3-(pyridin-4-yl)acrylonitriles (*E*/*Z* 6).**

a) from **1** with **3a**.

The crude residue solid was taken up with acetone to afford 0.35 g (23.6%) of **isonicotinic acid** (**9**).[9] On evaporation of acetone mother liquors the resulting residue was purified by flash chromatography on silica gel, eluting with a mixture of ether-light petroleum in 1:1 ratio, to give in the order: **benzotriazole** (**8**)[10] (0.58 g, 38.6%); ***E* 3-(1*H*-benzotriazol-1-yl)-3-(pyridin-4-yl)acrylonitrile (*E* 6)**: (0.43 g, 13.8%); mp 133-134 °C (ether); IR (cm^{-1}): 2220 (CN), 1610, 1590, 1550; UV (nm): λ_{max} 313, 262, 205; ^{1}H-NMR ($CDCl_3$): δ 8.90 (d, 2H, *J* = 6 Hz, H-3'+H-5'), 8.17 (dd, 1H, *J* = 6.5 and 1.8 Hz, H-4), δ 7.50 (d, 2H, *J* = 6 Hz, H-2'+H-6'), 7.46-7.38 (m, 2H, H-5+H-6), 6.63 (dd, 1H, *J* = 6.5 and 1.8 Hz, H-7), 6.42 (s, 1H, vinylic-H); ^{13}C-NMR ($CDCl_3$): δ 151.18 (C-3'+C-5'), 150.26 (*C*-CN), 146.94 (C-3a), 137.69 (C-1'), 131.78 (C-7a), 129.49 (C-6), 125.47 (C-5), 122.85 (C-2'+C-6'), 121.12 (C-4), 115.09 (CN), 110.98 (C-7), 92.60 (*HC*=C). MS *m/z* 247 (M^+). Anal. Calcd for $C_{14}H_9N_5$: C, 68.00; H, 3.67; N, 28.33. Found: C, 67.86; H, 3.81; N, 28.19; ***Z* 3-(1*H*-benzotriazol-1-yl)-3-(pyridin-4-yl)acrylonitrile (*Z* 6)**: (0.43 g, 13.8%); mp 155-156 °C (ether); IR (cm^{-1}): 2220 (CN), 1620, 1590, 1560; UV (nm): λ_{max} 296 infl., 253, 210; ^{1}H-NMR ($CDCl_3$): δ 8.78 (d, 2H, *J* = 5.8 Hz, H-3'+H-5'), 8.22 (dd, 1H, *J* = 8.4 and 1.6 Hz, H-4), δ 7.53 (m,

2H, H-5+H-6), 7.20 (d, 2H, *J* = 5.8 Hz, H-2'+H-6'), 7.08 (dd, 1H, *J* = 8.4 and 1.6 Hz, H-7), 6.14 (s, 1H, vinylic-H); ^{13}C-NMR ($CDCl_3$): δ 151.10 (C-3'+C-5'), 149.23 (*C*-CN), 146.13 (C-3a), 139.60 (C-1'), 132.14 (C-7a), 129.24 (C-6), 125.33 (C-5), 121.15 (C-2'+C-6'), 120.96 (C-4), 113.93 (CN), 110.73 (C-7), 95.48 (*HC*=C). MS *m/z* 247 (M^+). Anal. Calcd for $C_{14}H_9N_5$: C, 68.00; H, 3.67; N, 28.33. Found: C, 68.19; H, 3.70; N, 28.41; **2-(1*H*-benzotriazol-1-yl)acetamide** (**7**):[11] (0.40 g, 18%).

b) from **2** with **3a**.

The work up of the solid residue as under **a**) afforded in the order: **9 (**0.36 g, 24%), then by flash chromatography, ***E* 6** (0.60 g, 19%) and ***Z* 6** (0.44 g, 14%), identical to the above described compounds.

***E*/*Z* 2-(3-Imino-2-benzofuran-1(3*H*)-ylidene)acetonitriles (*E*/*Z* 20)**: The solid obtained was purified by flash chromatography on silica gel, eluting with a mixture of ether-light petroleum in 70:30 ratio, to give in the order ***Z* 2-(3-imino-2-benzofuran-1(3*H*)-ylidene)acetonitrile (*Z* 20)**: (0.63 g, 29.2%); mp 220-221 °C (acetone); IR (cm^{-1}): 3240 (NH), 2210 (CN), 1730, 1640, 1630, 1610, 1580; UV (nm): λ_{max} 320, 286 sh, 277, 226, 223, 210 sh; ^{1}H-NMR (DMSO-d_6): δ 11.61 (s, 1H, NH), 8.03 (d, 1H, *J* = 6.6 Hz, H-4), 7.82-7.65 (m, 3H, H-5+H-6+H-7), 5.95 (s, 1H, vinylic-H); ^{13}C-NMR (DMSO-d_6): δ 168.10 (C-1), 150.70 (C-3), 135.47 (C-3a), 133.16 (C-5), 131.97 (C-7), 129.05 (C-7a), 123.16 (C-4), 121.73 (C-6), 116.40 (CN), 70.43 (*CH*CN). MS *m/z* 170 (M^+). Anal. Calcd for $C_{10}H_6N_2O$: C, 70.58; H, 3.55; N, 16.46. Found: C, 70.68; H, 3.61; N, 16.35; **8** (1.42 g, 94%); ***E* 2-(3-imino-2-benzofuran-1(3*H*)-ylidene)acetonitrile (*E* 20)**: (0.60 g, 27.7%); mp 189-191 °C (acetone); IR (cm^{-1}): 3150 (NH), 2210 (CN), 1720, 1700, 1670, 1640, 1610, 1590; UV (nm): λ_{max} 321, 286 sh, 277, 227, 223, 207; ^{1}H-NMR (DMSO -d_6): δ 10.20 (s, 1H, NH), 8.31 (dd, 1H, *J* = 7.8 and 1.8 Hz, H-4), 7.93-7.75 (m, 3H, H-5+H-6+H-7), 5.46 (s, 1H, vinylic-H); ^{13}C-NMR (DMSO-d_6): δ 167.10 (C-1), 150.91 (C-3), 135.20 (C-3a), 134.10 (C-5), 132.79 (C-7), 130.02 (C-7a), 123.64 (C-4), 122.96 (C-6), 117.90 (CN), 72.74 (*CH*CN). MS *m/z* 170 (M^+). Anal. Calcd for $C_{10}H_6N_2O$: C, 70.58; H, 3.55; N, 16.46. Found: C, 70.41; H, 3.74; N, 16.40.

X-Ray structure determination

Crystal data of ***Z* 20**: white thin platelets, $C_{10}H_6N_2O$, M=170.2, monoclinic, space group $P2_1/n$, a=23.680(5), b = 5.208(5), c = 6.516(5) Å, β=90.00(5)°, V=804(1)Å^3, Z=4, D_{calc}= 1.407 g/cm^3, crystals dimensions 0.3 x 0.5 x 0.06 mm. Data were measured on a Enraf-Nonius CAD4 diffractometer equipped with graphite monochromated CuKα radiation. A total of 2867 reflections (1524 unique, 1162 unique observed) were collected in the θ range 3-70° using ω-2θ scan technique. The phase problem was solved by direct methods[12] and the structure was refined by full matrix least-squares cycles on all F^2 using 120 parameters.[13] All non hydrogen atoms were refined anisotropically, while hydrogens were introduced in

idealized positions. Final ΔF map was featureless. Final agreement is not fully satisfactory (R=0.19, Rw=0.53), due to scarce diffracting power of the extremely thin crystals, nevertheless the X-Ray analysis results confirm univocally the structural nature of ***Z* 20**.

Reaction of 2-(1*H*-benzotriazol-1-yl)acetonitrile (1) with 2-pyridinecarboxaldehyde (3b). A mixture of compound (**1)** (2.0 g, 12.6 mmol) with **3b** (1.35 g, 12.6 mmol) was submitted to reaction at rt for 120 h. Purification of the solid crude residue by flash chromatography on silica gel, eluting with a mixture of ether-light petroleum in 70:30 ratio, afforded: **8** (0.46 g, 30.6%); ***E* 3-(1*H*-benzotriazol-1-yl)-3-(pyridin-2-yl)acrylonitrile (*E* 14)**: (0.38 g, 12%); mp 144-145 °C (ether); IR (cm^{-1}): 2220 (CN), 1610, 1590, 1550; UV (nm): λ_{max} 323, 265, 210; ^{1}H-NMR ($CDCl_3$): δ 8.85 (d, 1H, *J* = 5 Hz, H-6'), 8.17 (d, 1H, *J* = 8.4 Hz, H-4), δ 8.07 (d, 1H, *J* = 8.4 Hz, H-7), 8.02 (s, 1H, vinylic-H), 7.87 (t, 1H, *J* = 8.4 Hz, H-6), 7.66-7.51 (m, 2H, H-3'+H-4'), 7.50-7.40 (m, 2H, H-5+H-5'); ^{13}C-NMR ($CDCl_3$): δ 151.16 (C-6'), 149.42 (C-2'), 146.41 (C-3a), 137.02 (*HC*=C), 136.88 (C-3'), 131.47 (C-7a), 129.25 (C-6), 125.78 (C-5), 125.36 (C-4'), 125.19 (C-5'), 120.57 (C-4), 113.06 (CN), 110.69 (C-7), 109.73 (*C*-CN). MS *m/z* 247 (M^+). Anal. Calcd for $C_{14}H_9N_5$: C, 68.00; H, 3.67; N, 28.33. Found: C, 67.91; H, 3.54; N, 28.56;

Reaction of 2-(1*H*-benzotriazol-1-yl)acetonitrile (1) with 4-nitrobenzaldehyde (3c). In a similar fashion as above from equimolar amonts of **1** (2.0 g, 12.6 mmol) and **3c** (1.90 g, 12.6 mmol) after purification of the crude solid residue by flash chromatography on silica gel, eluting with a mixture of ether-light petroleum in 1:1 ratio, we obtained: **7** (0.23 g, 15%); ***E* 2-(1*H*-benzotriazol-1-yl)-3-(4-nitrophenyl)acrylonitrile (*E* 16c)**[1] (1.63 g, 44.6%); ***E* 3-(1*H*-benzotriazol-1-yl)-3-(4-nitrophenyl)acrylonitrile (*E* 17c)**: (0.34 g, 9.3%); mp 118-120 °C (ether); IR (cm^{-1}): 2210 (CN), 1620, 1590, 1530; UV (nm): λ_{max} 274, 260 sh, 243; ^{1}H-NMR ($CDCl_3$): δ 8.44 (d, 2H, *J* = 8.6 Hz, H-3'+H-5'), 8.17 (dd, 1H, *J* = 8.8 and 1.8 Hz, H-4), δ 7.81 (d, 2H, *J* = 8.6 Hz, H-2'+H-6'), 7.56-7.40 (m, 2H, H-5+H-6), 6.64 (dd, 1H, *J* = 8.8 and 1.8 Hz, H-7), 6.42 (s, 1H, vinylic-H); ^{13}C-NMR ($CDCl_3$): δ 150.11 (*C*-CN), 149.70 (C-4'), 146.79 (C-3a), 136.01 (C-1'), 132.71 (C-7a), 130.51 (C-3'+C-5'), 129.53 (C-6), 125.48 (C-5), 124.28 (C-2'+C-6'), 120.98 (C-4), 115.23 (CN), 110.90 (C-7), 92.28 (*HC*=C). MS *m/z* 291 (M^+). Anal. Calcd for $C_{15}H_9N_5O_2$: C, 61.85; H, 3.11; N, 24.05. Found: C, 62.09; H, 3.02; N, 23.81; ***Z* 3-(1*H*-benzotriazol-1-yl)-3-(4-nitrophenyl)acrylonitrile (*Z* 17c)**: (0.38 g, 10.5%): mp 157-159 °C (acetone); IR (cm^{-1}): 2220 (CN), 1630, 1600, 1530; UV (nm): λ_{max} 289, 260 sh, 206; ^{1}H-NMR ($CDCl_3$): δ 8.32 (d, 2H, *J* = 8.4 Hz, H-3'+H-5'), 8.23 (d, 1H, *J* = 8.2 and 1.8 Hz, H-4), 7.60-7.45 (m, 4H, H-5+H-6+H-2'+H-6'), 7.07 (d, 1H, *J* = 8.2 and 1.8 Hz, H-7), 6.12 (s, 1H, vinylic-H), ^{13}C-NMR ($CDCl_3$): δ 149.87 (*C*-CN), 149.19 (C-4'), 146.11 (C-3a), 138.02 (C-1'), 132.09 (C-7a), 129.33 (C-6), 128.94 (C-3'+C-5'), 125.42 (C-5), 124.47 (C-2'+C-6'), 120.98 (C-4), 114.06 (CN), 110.76 (C-7), 95.19 (*HC*=C). MS *m/z* 291 (M^+). Anal.

Calcd for $C_{15}H_9N_5O_2$: C, 61.85; H, 3.11; N, 24.05. Found: C, 61.64; H, 3.23; N, 23.94; ***Z* 2-(1*H*-benzotriazol-1-yl)3-(4-nitrophenyl)acrylonitrile** (***Z* 16c**)[1] (0.60 g, 16.4%).

Reaction of 2-(2*H*-benzotriazol-2-yl)acetonitrile (2) with 4-nitrobenzaldehyde (3c): in a similar run as above from the reaction of compound (**2**) **(**2.0 g, 12.6 mmol) and **3c** (1.90 g, 12.6 mmol) after purification of the crude solid residue by flash chromatography on silica gel, eluting with a mixture of ether-light petroleum in 1:1 ratio, we obtained: **8** (0.30 g, 20%); ***E* 17c** (0.30 g, 8.2%); ***E* 18c**[1] (1.40 g, 38.4%); ***Z* 17c** (0.40 g, 11%).

Reactions of 2-(1*H*-benzotriazol-1-yl)acetonitrile (1) with 4-trifluoromethylbenzaldehyde (3d). Compounds (**1**) **(**2.0 g, 12.6 mmol) and **3d** (2.19 g, 12.6 mmol) were reacted under the above described conditions. Purification of the residual crude solid by flash chromatography on silica gel, eluting with a mixture of ether-light petroleum in 1:1 ratio, afforded: **8** (0.37 g, 25%); ***E* 16d**[1] (2.70 g, 68%); ***Z* 3-(1*H*-benzotriazol-1-yl)-3-(4-trifluoromethyl)acrylonitrile** (***Z* 17d**) (0.12 g, 3%); mp 110-112 °C; IR (cm^{-1}): 2230 (CN), 1635, 1530; UV (nm): λ_{max} 270, 206; ^{1}H-NMR ($CDCl_3$): δ 8.21 (d, 1H, *J* = 8.2 and 1.8 Hz, H-4), 7.74 (d, 2H, *J* = 8.2 Hz, H-2'+H-6'), 7.60-7.46 (m, 2H, H-5+H-6), 7.44 (d, 2H, *J* = 8.2 Hz, H-3'+H-5'), 7.04 (d, 1H, *J* = 8.2 and 1.8 Hz, H-7), 6.03 (s, 1H, vinylic-H); ^{13}C-NMR ($CDCl_3$): δ 150.09 (*C*-CN), 146.25 (C-3a), 135.79 (C-1'), 134.18 (C-4'), 132.29 (C-7a), 129.22 (C-6), 126.27 (C-2'+C-6'), 126.46 (C-3'+C-5'), 125.31 (C-5), 121.03 (C-4), 114.27 (CN), 110.87 (C-7), 94.06 (*HC*=C). MS *m/z* 314 (M^+). Anal. Calcd for $C_{16}H_9N_4F_3$: C, 61.15; H, 2.89; N, 17.83, F, 18.14. Found: C, 61.32; H, 3.02; N, 17.67, F, 18.17.

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REFERENCES

1. P. Sanna, A. Carta, and M. E. Rahbar Nikookar, *Eur. J. Med. Chem.*, 2000, **35**, 535.
2. P. Sanna, A. Carta, L. Gherardini, and M. E. Rahbar Nikookar, *Il Farmaco*, 2002, **57**, 79.
3. A. R. Katritzky, *Il Farmaco*, 1988, **43**, 1175.
4. A. R. Katritzky, S. Rachwal, and G. J. Hitchings, *Tetrahedron*, 1991, **47**, 2683.
5. A. R. Katritzky, J. Jiang, J. V. Greenhil, and P. J. Steel, *J. Chem. Soc., Perkin Trans. 1*, 1992, 3055.
6. P. Sanna, A. Carta, G. Paglietti, A. Bacchi, and G. Pelizzi, *J. Heterocycl. Chem.*, 1997, **34**, 97.
7. G. Paglietti, P. Sanna, A. Carta, F. Sparatore, I. Vazzana, A. Peana, and M. Satta, *Il Farmaco*, 1994, **49**, 693.
8. L. Collins and S. G. Franzblau, *Antimicrob. Agents Chemother.*, 1997, **41**, 1004.

9. G. Black, E. Depp, and B. B. Corson, *J. Org. Chem*., 1949, **14**, 14.
10. R. E. Damschroder and W. D. Peterson, *Org. Synth*., 1940, **20**, 16.
11. A. R. Katritzky, J. Chen, and Z. Yang, *J. Org. Chem*., 1995, **60**, 5638.
12. SIR97 – A. Altomare, M. C. Burla, M. Camalli, G. L. Cascarano, C. Giacovazzo, A. Guagliardi, A. G. G. Moliterni, G. Polidori, and R. Spagna, *J. Appl. Cryst.*, 1999, **32**, 115.
13. SHELXL97 – G. M. Sheldrick, Program for Crystal Structure Analysis, *Institut fur Anorganische Chemie der Universitat*, Gottingen, Germany, 1998.