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Reaction of Benzo[*b*]furan and 1-Acylindoles with Iodine Azide

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Reaction of benzo[*b*]furan with iodine azide gives in high yield a mixture of *cis*- and *trans*-2,3-diazido-2,3-dihydrobenzo[*b*]furans, both of which, upon treatment with alkali, are converted to 3-azidobenzo[*b*]furan. Similar reaction of 1-benzoyl- and 1-tosyl-indoles with iodine azide affords high yields of *cis*- and *trans*-1-benzoyl- and 1-tosyl-2,3-diazidoindolines. Stereochemical assignment of the adducts is made on the basis of nuclear magnetic resonance spectroscopy.

Keywords——abnormal addition of iodine azide; stereochemistry; elimination of HN_3; 1,3-dipolar cycloaddition; dimerization

Iodine azide is known to undergo addition to a number of olefins with stereo- and regiospecificity to give β-iodoazides.[2)] Recently we have reported the reaction of benzo[*b*]furan and 1-acylindoles with iodine azide which affords *cis*- and *trans*-2,3-diazido-2,3-dihydrobenzo[*b*]furans[3)] and 1-acyl-2,3-diazidoindolines,[4)] respectively. The purposes of these studies were to determine the role of the hetero atom in the addition reaction of iodine azide and to explore the possible usefulness of the reaction as a general method for direct introduction of azido function to these heterocycles.[5)] In this paper we wish to report in some detail the reaction of benzo[*b*]furan and 1-benzoyl- and 1-tosyl-indoles with iodine azide and some chemical properties of the novel reaction products.

Treatment of benzo[*b*]furan (**1**) with iodine azide (prepared *in situ* in dry acetonitrile) at 0° for 1 hr and then at room temperature for 3 hr gave 93% yield of an oily mixture of two isomeric adducts which could be separated by preparative thin-layer chromatography (TLC) and were assigned the gross structure 2,3-diazido-2,3-dihydrobenzo[*b*]furan (**2** and **3**) on the basis of the spectral (see Experimental) and chemical evidence. Refluxing **2** and **3** with dimethyl acetylenedicarboxylate in toluene for 6 hr gave crystalline 1:2 cycloadducts **4** and **5**, respectively. The stereochemistry of **2** and **3** was readily ascertained by an examination of the nuclear magnetic resonance (NMR) spectra and their behavior toward alkali. The diazides **2** and **3** showed large *cis*-vicinal coupling constant ($J_{2,3}$=7 Hz) and small *trans*-vicinal coupling constant ($J_{2,3}$=1.5 Hz),[6)] respectively. Treatment of **2** and **3** with 15% ethanolic potassium hydroxide gave oily 3-azidobenzo[*b*]furan (**6**) in 83 and 87% yields, respectively, but the reaction proceeded appreciably faster with the *cis*-isomer **2** than with the *trans*-isomer **3**; after 1 hr at room temperature **2** was completely converted to **6**, while **3** was converted to **6** only after *ca.* 24 hr at room temperature. These behaviors closely resemble those of *cis*- and *trans*-2,3-dichloro-2,3-dihydrobenzo[*b*]furans toward base, in which 3-chlorobenzo[*b*]furan was formed.[6b)]

1) Location: *133-1, Yamada-kami, Suita, Osaka, 565, Japan.*
2) A. Hassner, *Accounts Chem. Res.*, **4**, 9 (1971) and references therein.
3) S. Kwon, T. Okada, M. Ikeda, and Y. Tamura, *Heterocycles*, **6**, 33 (1977).
4) Y. Tamura, S. Kwon, F. Tabusa, and M. Ikeda, *Tetrahedron Lett.*, **1975**, 3291.
5) A similar treatment of benzo[*b*]thiophene with iodine azide in dry acetonitrile led to an explosion.
6) *a*) M.P. Mertes and L.J. Powers, *J. Org. Chem.*, **36**, 1805 (1971); *b*) E. Baciocchi, S. Clementi, and G.V. Sebastiani, *J. Heterocyclic Chem.*, **14**, 359 (1977).

The structure of **6** was deduced on the basis of its spectral and chemical properties. Thus, its infrared (IR) spectrum displayed a strong azide band at 2100 cm^{-1}. The NMR spectrum showed a singlet due to H-2 at δ 7.50[7] and precludes the possibility of 2-azidobenzo[*b*]furan from consideration. Refluxing **6** with dimethyl acetylenedicarboxylate in toluene for 1 hr gave a crystalline 1:1 adduct **7**. Reduction of **6** with sodium borohydride in isopropyl alcohol afforded a dimeric compound **8** which formed the monoacetate **9** by treatment with acetic anhydride and sodium acetate. Compound **8** had a molecular formula $C_{16}H_{11}NO_2$ and showed its molecular ion peak at *m/e* 249 in its mass spectrum, IR bands at 3370 and 3310 cm^{-1} (NH_2), and a singlet (1H) at δ 7.94 (H-2) in its NMR spectrum. The formation of **8** can be rationalized as illustrated in Chart 1; the initially formed 3-aminobenzo[*b*]furan may undergo Aldol-type condensation followed by rearomatization to lead to **8**.

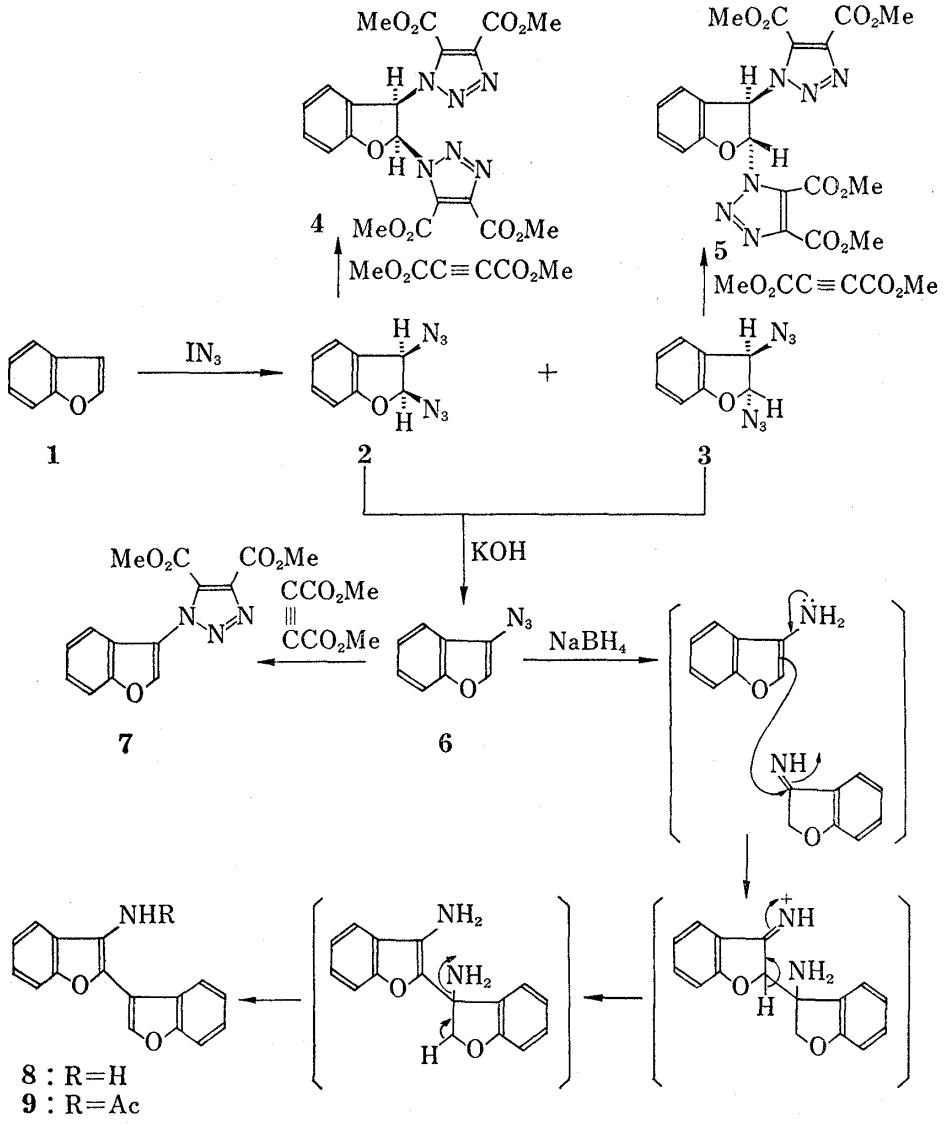

Chart 1

In a similar manner, the reaction of 1-benzoyl- (**10a**) and 1-tosyl-indoles (**10b**) with iodine azide afforded 2,3-diazidoindolines **11a, b** and **12a, b**, respectively, whose structures

7) The H-2 and H-3 signals (in $CDCl_3$) of benzo[*b*]furan appear at δ 7.54 and 6.86, respectively. T.J. Batterham, "NMR Spectra of Simple Heterocycles," John Wiley and Sons, Inc., New York, 1973, p. 375.

were assigned on the basis of the spectral and chemical evidence. For example, **11a** exhibits IR band at 2100 (N_3) and 1645 cm^{-1} (C=O) and the NMR signals due to the H-2 and H-3 protons at δ 5.97 and 4.98, respectively. Reduction of **11a** or **12a** with lithium aluminum hydride in ether gave 1-benzylindole (**13**). Refluxing **11a** and **12a** with dimethyl acetylene-

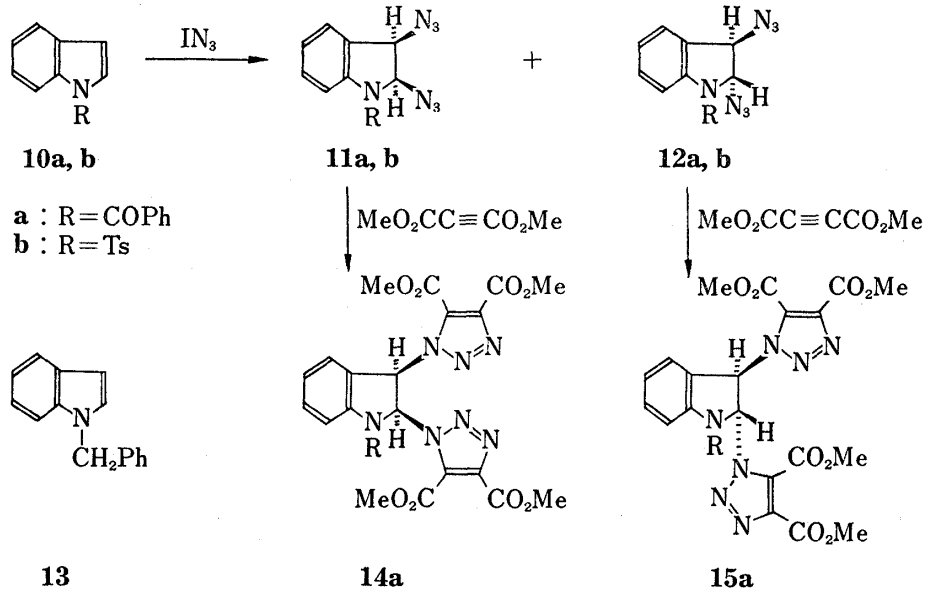

Chart 2

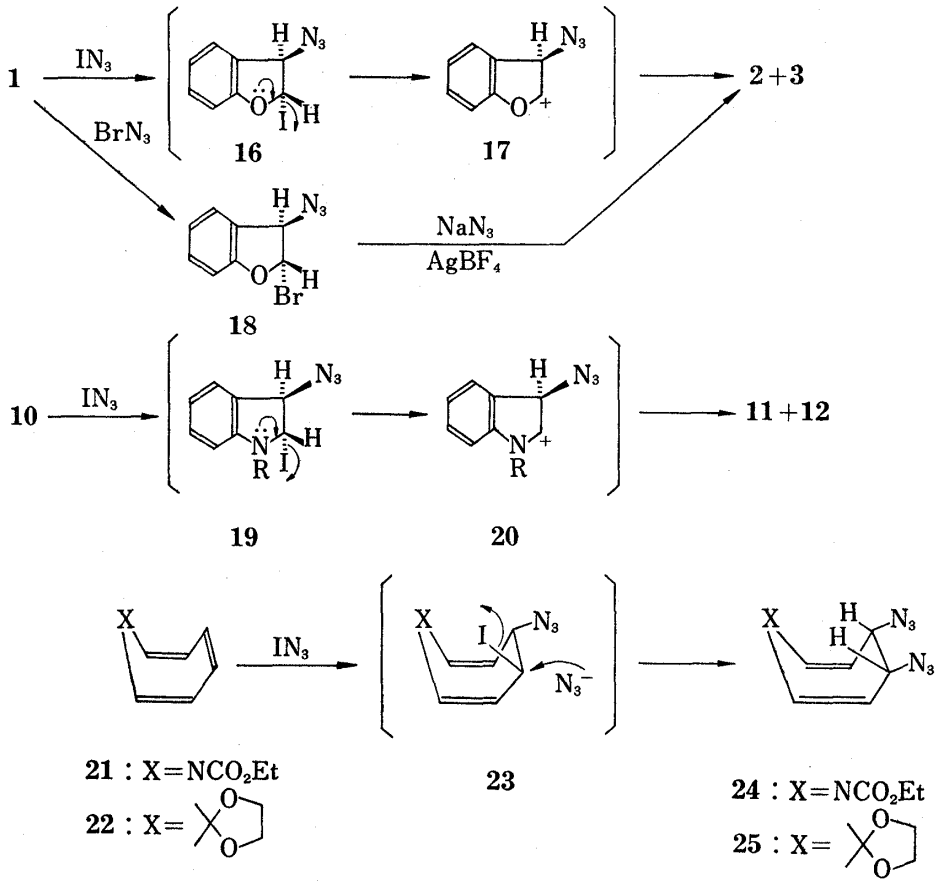

Chart 3

dicarboxylate in toluene gave the corresponding 1: 2 cycloadducts **14a** and **15a**. The stereochemical relationship of two azido groups in the 2,3-diazidoindolines is ascertained by an examination of the NMR spectra; **11a** and **11b** indicated the coupling constants ($J_{2,3}$) of 7 Hz, while **12a** and **12b** showed the coupling constants ($J_{2,3}$) of 0 Hz. These coupling constants were in good agreement with the reported values for *cis*- and *trans*-vicinal coupling in 1-acylindolines,[8] respectively.

A mechanistic rationalization of the non-stereospecific formation of the diazides is based on the assumption that the initially formed adducts **16** and **19** undergo carbon-iodine bond cleavage to give carbonium ions **17** and **20**. The ions may be then attacked by azide anion to give a mixture of the *cis*- and *trans*-diazides. Attempts to obtain 1: 1 adducts **16** and **19** have thus far proved unsuccessful; for example, the reaction of equimolar quantities of **1** and iodine azide gave the corresponding diazides **2** and **3** and starting material. However, strong support for the proposed mechanism was derived from the reaction of *trans*-3-azido-2-bromo-2,3-dihydrobenzo[*b*]furan (**18**)[9] with sodium azide in the presence of silver ion, which afforded a mixture of **2** and **3** though in lower yields. No reaction occurred in the absence of silver ion.

These findings are in contrast to the observation of Sasaki and coworkers[10] that reaction of 1-ethoxycarbonyl-1(1H)-azepine (**21**) and tropone ethylene ketal (**22**) with iodine azide produces exclusively the 1,2-*cis*-diazides **24** and **25**, respectively, probably by the S_N2 attack of the azide ion to the initially formed *trans*-iodoazides (**23**). In our cases, the cleavage of the carbon-iodine bond in **16** and **19** may be facilitated by the participation of the heteroatom.

Experimental[11]

Material——Benzo[*b*]furan (**1**) was obtained commercially. 1-Benzoylindole (**10a**) was prepared according to the procedure of Welstead, Stauffer, and Sancilio.[12] 1-*p*-Toluenesulfonylindole (**10b**) was prepared by the method of Bowman and coworkers.[13]

***cis*- and *trans*-2,3-Diazido-2,3-dihydrobenzo[*b*]furans (2 and 3)**——A solution of **1** (0.59 g, 5 mmol) in dry acetonitrile (10 ml) was added dropwise to a stirred solution of IN_3 [prepared *in situ* from ICl (1.625 g, 10 mmol) and NaN_3 (0.975 g, 15 mmol)] in dry acetonitrile (10 ml) at 0—5°. After the reaction mixture was stirred at the same temperature for 2 hr and then at room temperature for 3 hr, the mixture was diluted with H_2O and extracted with ether. The extract was washed with 5% $Na_2S_2O_3$ solution and H_2O, dried ($MgSO_4$), and concentrated *in vacuo* to give a mixture (940 mg, 93%) of **2** and **3** in a ratio of *ca.* 1: 1 (by NMR spectroscopy). The products were separated by preparative TLC using silica gel and *n*-hexane as solvent to give oily *cis*-diazide **2** (313 mg, 31%) and oily *trans*-diazide **3** (434 mg, 43%).

2: IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 2100 (N_3). NMR ($CDCl_3$) δ: 7.5—6.85 (m, 4H, arom. protons), 5.83 (d, 1H, J=7 Hz, H-2) and 4.90 (bd, 1H, J=7 Hz, H-3).

3: IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 2100 (N_3). NMR ($CDCl_3$) δ: 7.7—6.9 (m, 4H, arom. protons), 5.76 (d, 1H, J=1.5 Hz, H-2), and 4.61 (bs, 1H, H-3).

***cis*-2,3-Di(4,5-dimethoxycarbonyl-1,2,3-triazol-1-yl)-2,3-dihydrobenzo[*b*]furan (4)**——A solution of **2** (250 mg, 1.27 mmol) and dimethyl acetylenedicarboxylate (450 mg, 3.18 mmol) in toluene (10 ml) was heated under reflux for 8 hr. The solvent was removed *in vacuo* and the residual solid was recrystallized from methanol to give **4** (300 mg, 50%) as colorless crystals, mp 172—174°. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1740 (C=O). NMR (DMSO-d_6) δ: 7.7—7.0 (m, 6H, arom. protons, H-2 and H-3), 3.91 (s, 3H, OCH_3), 3.89 (s, 3H, OCH_3), 3.83 (s, 3H, OCH_3), and 3.80 (s, 3H, OCH_3). *Anal.* Calcd. for $C_{20}H_{18}N_6O_9$: C, 49.38; H, 3.73; N, 17.28. Found: C, 49.17; H, 3.71; N, 17.45.

8) F.A.L. Anet and J.M. Muchowski, *Chem. Ind.* (London), **1963**, 81.
9) T. Okuyama, K. Kunugiza, and T. Fueno, *Bull. Chem. Soc. Jpn.*, **47**, 1267 (1974).
10) T. Sasaki, K. Kanematsu, and Y. Yukimoto, *J. Org. Chem.*, **37**, 890 (1972).
11) All melting points are uncorrected. The NMR spectra were recorded with a Hitachi R-20A (60 MHz) or R-22 (90 MHz) spectrometer with tetramethylsilane as internal standard, IR spectra with a Hitachi EPI-G2 spectrophotometer, and mass spectra with a Hitachi RMU-6D instrument with a direct inlet system at 70 eV. Preparative TLC was carried out on Merck Silica gel GF_{254} and Alumina PF_{254}.
12) W.J. Welstead, Jr., H.F. Stauffer, Jr., and L.F. Sancilio, *J. Heterocyclic Chem.*, **17**, 544 (1974).
13) R.E. Bowman, D.D. Evans, and P.J. Islip, *Chem. Ind.* (London), **1971**, 33.

***trans*-2,3-Di(4,5-dimethoxycarbonyl-1,2,3-triazol-1-yl)-2,3-dihydrobenzo[*b*]furan (5)**——Using a similar procedure described above for preparation of **4**, the cycloadduct **5** (108 mg, 18%) was obtained from **3** (250 mg) and dimethyl acetylenedicarboxylate (450 mg), mp 67—69° (from methanol–H_2O). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1740 (C=O). NMR (DMSO-d_6) δ: 7.6—7.0 (m, 6H, arom. protons, H-2 and H-3), 3.91 (s, 9H, $3\times OCH_3$), and 3.82 (s, 3H, OCH_3). *Anal.* Calcd. for $C_{20}H_{18}N_6O_9$: C, 49.38; H, 3.73; N, 17.28. Found: C, 48.87; H, 3.73; N, 17.28.

3-Azidobenzo[*b*]furan (6)——1) From **2**: A solution of **2** (200 mg) and KOH (250 mg) in ethanol (5 ml) was stirred at room temperature for 1 hr (the reaction was followed by TLC). The reaction mixture was poured into H_2O and extracted with methylene chloride. The extract was washed with H_2O, dried ($MgSO_4$), and concentrated *in vacuo*. The residual oil was purified by passing through a short column on silica gel with petroleum ether (bp 30—60°) to give **6** (131 mg, 83%) as an oil. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 2100 (N_3). NMR ($CDCl_3$) δ: 7.75—7.2 (m, 4H, arom. protons) and 7.50 (s, 1H, H-2).

2) From **3**: A solution of **3** (200 mg) and KOH (250 mg) in ethanol (5 ml) was stirred at room temperature for 24 hr. Work up as described above gave **6** (137 mg, 87%).

3-(4,5-Dimethoxycarbonyl-1,2,3-triazol-1-yl)benzo[*b*]furan (7)——A solution of **6** (300 mg) and dimethyl acetylenedicarboxylate (320 mg) in toluene (10 ml) was refluxed for 1 hr. After the solvent was removed *in vacuo*, the residue was purified by preparative TLC using alumina and benzene as solvent to give **7** (125 mg, 22%), mp 123—124° (from methanol). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1730 (C=O). NMR ($CDCl_3$) δ: 8.16 (s, 1H, H-2), 7.8—7.35 (m, 4H, arom. protons), 4.04 (s, 3H, OCH_3), and 3.94 (s, 3H, OCH_3). *Anal.* Calcd. for $C_{14}H_{11}N_3O_5$: C, 55.81; H, 3.68; N, 13.95. Found: C, 55.54; H, 3.65; N, 13.97.

Reduction of 6 with $NaBH_4$——A mixture of **6** (750 mg) and $NaBH_4$ (500 mg) in isopropyl alcohol (30 ml) was stirred at room temperature overnight. The reaction mixture was poured into H_2O and extracted with methylene chloride. The extract was washed with H_2O, dried ($MgSO_4$), and concentrated. The residue was purified by preparative TLC using silica gel and chloroform as solvent to give 3-amino-2-(benzo[*b*]furan-3-yl)benzo[*b*]furan (**8**) (170 mg, 15%), mp 90—92° (*n*-hexane–benzene). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3370 and 3310 (NH_2). NMR ($CDCl_3$) δ: 8.3—8.1 (m, 1H, arom. proton), 7.94 (s, 1H, H-2), 7.6—7.0 (m, 7H, arom. protons), and 3.40 (b, 2H, NH_2). MS *m/e*: 249 (M^+). *Anal.* Calcd. for $C_{16}H_{11}NO_2$: C, 77.09; H, 4.45; N, 5.62. Found: C, 76.91; H, 4.55; N, 5.66.

Acetylation of 8——A mixture of **8** (50 mg) and sodium acetate (40 mg) in acetic anhydride (3 ml) was heated at 60° for 30 min. After cooling, the precipitated crystals were collected and washed with H_2O. Recrystallization from methanol gave colorless crystals of 3-acetamido-2-(benzo[*b*]furan-3-yl)benzo[*b*]furan (**9**) (46 mg), mp 224.5—226°. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3400 (NH) and 1680 (C=O). NMR (DMSO-d_6) δ: 8.45 (s, 1H, H-2), 8.05—8.25 (m, 1H, arom. proton), 7.2—7.85 (m, 7H, arom. protons), and 2.18 (s, 3H, CH_3). *Anal.* Calcd. for $C_{18}H_{13}NO_3$: C, 74.21; H, 4.50; N, 4.81. Found: C, 74.09; H, 4.50; N, 4.75.

***cis*- and *trans*-1-Benzoyl-2,3-diazidoindolines (11a and 12a)**——Using a similar procedure described for preparation of **2** and **3**, a mixture (1.50 g, 80%) of **11a** and **12a** (the ratio=*ca.* 2:7) was obtained from **10a** (1.11 g). The crude mixture was diluted with ether and an insoluble solid was collected and recrystallized from methanol to give **11a** (259 mg, 17%), mp 136—138°. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 2100 (N_3) and 1645 (C=O). NMR ($CDCl_3$) δ: 7.7—6.9 (m, 9H, arom. protons), 5.97 (d, 1H, J=7 Hz, H-2), and 4.98 (bd, 1H, J=7 Hz, H-3). *Anal.* Calcd. for $C_{15}H_{11}N_7O$: C, 59.01; H, 3.63; N, 32.12. Found: C, 58.89; H, 3.62; N, 32.07.

The mother liquor was evaporated and the residual oil was purified by silica gel column chromatography with *n*-hexane–ether (5:1) to give **12a** (961 mg, 63%). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 2100 (N_3) and 1645 (C=O). NMR ($CDCl_3$) δ: 7.7—6.9 (m, 9H, arom. protons), 5.82 (s, 1H, H-2), and 4.54 (bs, 1H, H-3).

***cis*- and *trans*-1-*p*-Toluenesulfonyl-2,3-diazidoindolines (11b and 12b)**——Using a similar procedure described for preparation of **2** and **3**, a mixture (1.33 g, 92%) of **11b** and **12b** (the ratio=*ca.* 1:1) was obtained from **10b** (1.36 g). The products were separated by fractional recrystallization from methanol to give the more soluble *cis*-diazide **11b** (675 mg, 38%), mp 95—96°, and the less soluble *trans*-diazide **12b** (870 mg, 49%), mp 113—114°.

11b: IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 2110 (N_3), 1365 and 1165 (SO_2). NMR ($CDCl_3$) δ: 7.9—7.15 (m, 8H, arom. protons), 5.77 (d, 1H, J=7 Hz, H-2), 4.54 (bd, 1H, J=7 Hz, H-3), and 2.39 (s, 3H, toluene ring CH_3). *Anal.* Calcd. for $C_{15}H_{13}N_7O_2S$: C, 50.70; H, 3.69; N, 27.60. Found: C, 50.55; H, 3.70; N, 27.91.

12b: IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 2100 (N_3), 1365 and 1165 (SO_2). NMR ($CDCl_3$) δ: 7.9—7.1 (m, 8H, arom. protons), 5.99 (s, 1H, H-2), 4.34 (bs, 1H, H-3), and 2.35 (s, 3H, toluene ring CH_3). *Anal.* Calcd. for $C_{15}H_{13}N_7O_2S$: C, 50.70; H, 3.69; N, 27.60. Found: C, 50.53; H, 3.71; N, 27.37.

Reduction of 11a or 12a with $LiAlH_4$——A mixture of **11a** (60 mg) and $LiAlH_4$ (40 mg) in ether (10 ml) was stirred at room temperature for 3 hr. The reaction mixture was treated with ethyl acetate and H_2O to decompose excess $LiAlH_4$ and extracted with ether. The extract was dried ($MgSO_4$) and concentrated to give 1-benzylindole (**13**) (31 mg) which was identified by a direct comparison of its IR spectrum with that of an authentic sample.

A similar treatment of **12a** (60 mg) gave **13** (30 mg).

1-Benzoyl-*cis*-2,3-di(4,5-dimethoxycarbonyl-1,2,3-triazol-1-yl)indoline (14a)——Using a similar precedure described for **4**, **14a** (477 mg, 81%) was obtained from **11a** (305 mg), mp 115—118° (from methanol–H_2O). IR ν_{max}^{KCl} cm^{-1}: 1730 (C=O) and 1670 (C=O). NMR ($CDCl_3$) δ: 7.5—7.0 (m, 11H, arom. protons, 2-H,

and 3-H), 3.98 (s, 3H, OCH_3), 3.90 (s, 3H, OCH_3), 3.84 (s, 3H, OCH_3), and 3.73 (s, 3H, OCH_3). *Anal.* Calcd. for $C_{27}H_{23}N_7O_9$: C, 55.01; H, 3.93; N, 16.63. Found: C, 54.80; H, 3.95; N, 16.03.

1-Benzoyl-*trans*-2,3-di(4,5-dimethoxycarbonyl-1,2,3-triazol-1-yl)indoline (15a)——Using a similar procedure described for **4**, **15a** (448 mg, 76%) was obtained from **12a** (305 mg), mp 98—101° (from methanol–H_2O). IR ν_{max}^{KCl} cm^{-1}: 1730 (C=O) and 1670 (C=O). NMR ($CDCl_3$) δ: 7.6—6.8 (m, 11H, arom. protons, 2-H, and 3-H), 3.97 (s, 3H, OCH_3), 3.93 (s, 3H, OCH_3), 3.87 (s, 3H, OCH_3), and 3.85 (s, 3H, OCH_3). *Anal.* Calcd. for $C_{27}H_{23}N_7O_9$: C, 55.01; H, 3.93; N, 16.63. Found: C, 54.72; H, 3.95; N, 16.63.

Reaction of 18 with NaN_3 in the Presence of Silver Ion——To a solution of **18**[9] (300 mg) in dry acetonitrile (20 ml) were added NaN_3 (200 mg) and $AgBF_4$ (300 mg) all at once at room temperature with stirring. The reaction mixture was stirred at room temperature for 3 hr and filtered. The filtrate was poured into H_2O and extracted with ether. The extract was washed with H_2O, dried ($MgSO_4$), and concentrated. The residual oil was submitted to preparative TLC on silica gel with *n*-hexane to give **2** (55 mg) and **3** (67 mg), which were identified by a comparison of their IR spectra with those of authentic samples.

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