NEW SYNTHESIS OF BENZO[*a*]PHENAZINES BASED ON ACID PROMOTED RING OPENING OF THE BENZOTRIAZOLE MOIETY

Alan R. Katritzky,[a*] Abd El Rachman Ferwanah,[b] Yasuhisa Matsukawa,[a]
Peter J. Steel,[c] and Sergey N. Denisenko[a]

[a] *Center for Heterocyclic Compounds, Department of Chemistry, University of Florida, Gainesville, Florida 32611-7200, USA*
[b] *Al-Azhar University of Gaza, P. O. Box 1277, Gaza, Palestine*
[c] *Department of Chemistry, University of Canterbury, Christchurch, New Zealand*

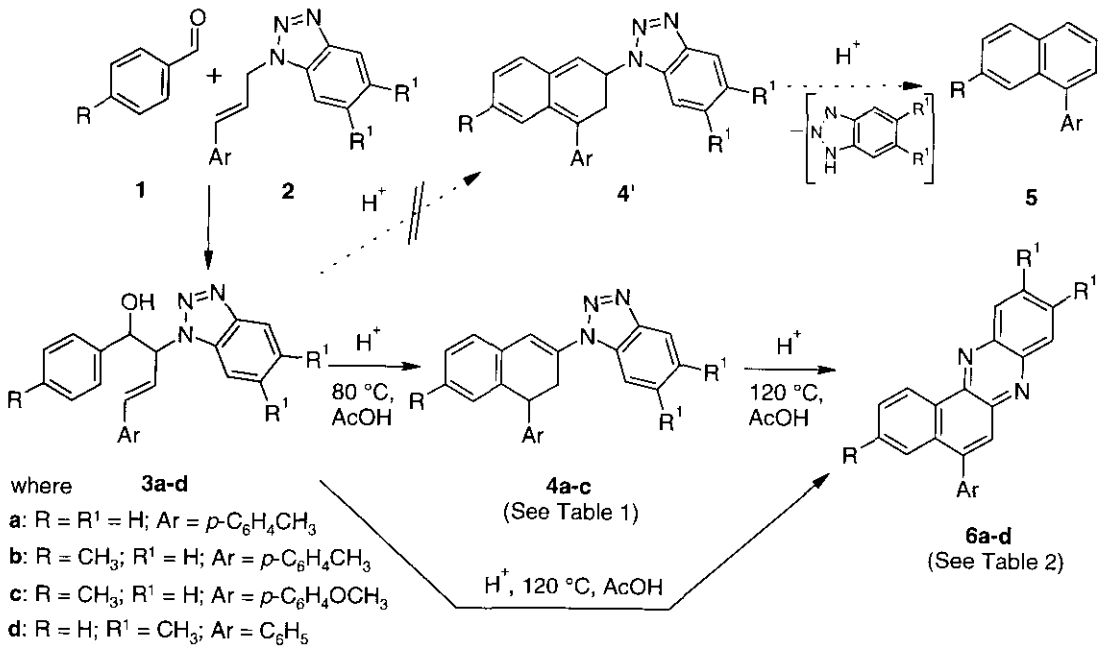
Abstract — Syntheses of benzo[*a*]phenazines (**6a-d**) have been accomplished based on an acid promoted tandem benzotriazole ring-opening / ammonia extrusion procedure. Compounds (**6a-d**) are thus accessible directly from 3-(benzotriazol-1-yl)-1,4-diaryl-1-buten-4-ols (**3a-d**) in one-pot reaction sequences or from the intermediate 3,4-dihydronaphthalenes (**4a-c**). This constitutes a new type of benzotriazole ring transformation.

RESULTS AND DISCUSSION

In continuation of our investigations of the synthetic utilities of *N*-substituted benzotriazoles,[1] we have studied potential pathways to the naphthalene ring system. Recently described syntheses of 1,4-diaryl-3-(1*H*-benzotriazolyl)-4-hydroxybutenes (**3**)[2] potentially offer a versatile route to naphthalenes (**5**) with various substituents in both aromatic rings (Scheme 1). The benzotriazole residue should act both as an anion stabilizing group in the transformation of **2** to **3**, and as a leaving group in the aromatization of **4′** to **5**.

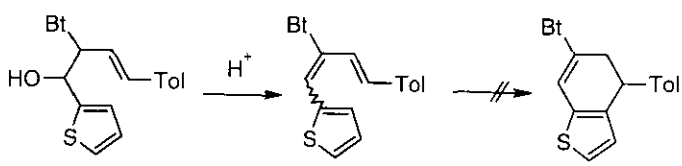
To our surprise, refluxing compounds (**3a-d**) in acetic acid in the presence of 10 equivalents of sulfuric acid gave high yields of benzo[*a*]phenazines (**6a-d**) (Scheme 1, Table 2). The structure of **6a** (see Table 2) was confirmed by X-Ray crystallography (Figure 1). As expected, the benzo[*a*]phenazine ring system is

planar (mean deviation from the plane = 0.012(3) Å), while the plane of the attached tolyl substituent is inclined to this at an angle of 65.8(2) °.



Scheme 1

The corresponding 3,4-dihydronaphthalenes (**4a-c**) were formed in this reaction as isolable intermediates (Scheme 1). Heating of alcohols (**3a-c**) at 80 °C in acetic acid in the presence of sulfuric acid for 3 hours produced compounds (**4a-c**), which were isolated and fully characterized (Table 1). The structures of compounds (**4a-c**) were established by both NMR and CHN analysis. Subsequent heating of **4a-c** at 120 °C for 5 hours led cleanly to **6a-c**.



Scheme 2

The transformation of **3** to **6** proceeded in good yield when R = H or CH_3, but we failed to isolate products if the substituent R in (**3**) was Cl or Br. Treatment of the thiophene derivative (**7**) under the same conditions led to the mixture of dienes (**8**) in ratio ~ 1 : 1 of (*E,Z*)-stereoisomers (Scheme 2). No further electrocyclic rearrangement of **8** to **9** was detected.

Table 1. Synthesis of 3,4-dihydronaphthalenes (**4**) and diene (**8**)

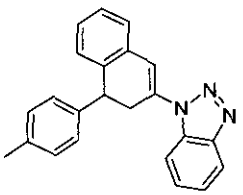
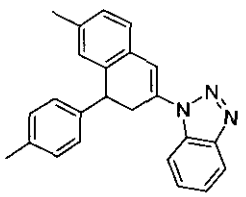
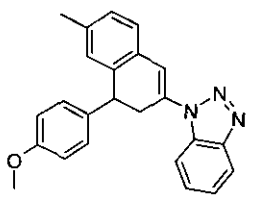
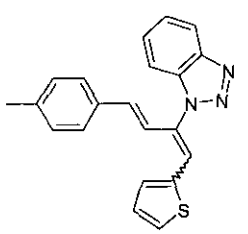
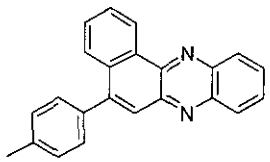
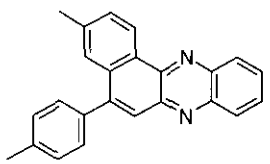
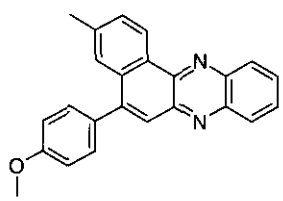
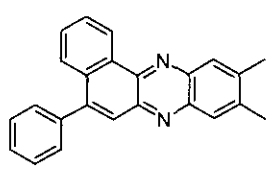
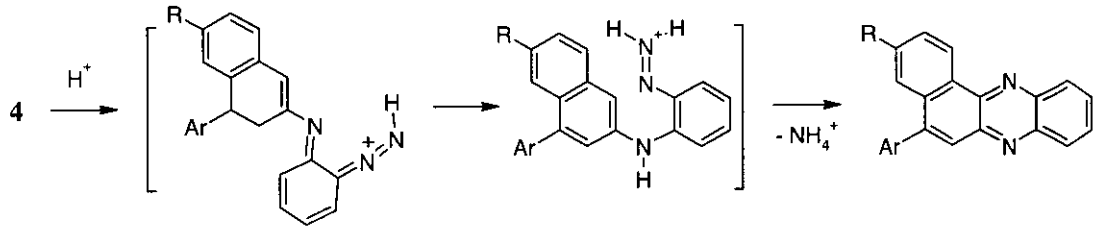
Entry (Yield)	Product	^{1}H- NMR and ^{13}C-NMR data ($CDCl_3$), δ
4a (76%)		^{1}H-NMR: 8.11 (d, J = 8.3 Hz, 1H), 7.75 (d, J = 8.5 Hz, 1H), 7.54 (dd, J = 7.7 Hz, J = 7.4 Hz, 1H), 7.42 (dd, J = 7.8 Hz, J = 7.4 Hz, 1H), 7.34-7.10 (m, 7H), 7.03 (s, 1H), 7.00 (d, J = 7.4 Hz, 1H), 4.49 (dd, J = 8.7 Hz, J = 8.2 Hz, 1H), 3.65-3.42 (m, 2H), 2.35 (s, 3H). ^{13}C-NMR: 146.4, 139.8, 136.9, 136.5, 134.6, 132.5, 131.7, 129.3 (2C), 128.3, 128.1 (2C), 128.0 (2C), 127.3, 127.2, 124.3, 120.4, 118.2, 111.3, 44.0, 34.3, 21.0
4b (67%)		^{1}H-NMR: 8.08 (d, J = 8.2 Hz, 1H), 7.70 (d, J = 8.2 Hz, 1H), 7.50 (dd, J = 7.1 Hz, J = 8.0 Hz, 1H), 7.38 (dd, J = 7.4 Hz, J = 7.7 Hz, 1H), 7.22-7.09 (m, 3H), 7.07 (d, J = 7.6 Hz, 1H), 6.98 (s, 1H), 6.81 (s, 1H), 4.42 (dd, J = 8.0 Hz, J = 8.2 Hz, 1H), 3.60-3.35 (m, 2H), 2.32 (s, 3H), 2.27 (s, 3H). ^{13}C-NMR: 146.3, 140.0, 138.4, 136.7, 136.4, 133.5, 131.7, 129.8, 129.3 (2C), 128.9, 128.1 (2C), 127.9, 127.8, 127.3, 124.3, 120.3, 118.4, 111.2, 44.0, 34.5, 21.4, 21.0
4c (60%)		^{1}H-NMR: 8.09 (d, J = 8.2 Hz, 1H), 7.70 (d, J = 8.2 Hz, 1H), 7.51 (dd, J = 7.1 Hz, J = 8.0 Hz, 1H), 7.39 (dd, J = 7.4 Hz, J = 7.7 Hz, 1H), 7.28-7.14 (m, 3H), 7.08 (d, J = 7.5 Hz, 1H), 6.99 (s, 1H), 6.87 (d, J = 8.2 Hz, 2H), 6.81 (s, 1H), 4.42 (dd, J = 7.9 Hz, J = 8.0 Hz, 1H), 3.79 (s, 3H), 3.60-3.35 (m, 2H), 2.29 (s, 3H). ^{13}C-NMR: 158.5, 146.5, 138.4, 136.9, 135.1, 133.5, 132.0, 129.8, 129.2 (2C), 128.9, 127.9, 127.8, 127.3, 124.3, 120.3, 118.4, 114.1 (2C), 111.3, 55.2, 43.7, 34.6, 21.5
8 (76% for two iso-mers)		^{1}H-NMR: 8.16 (d, J = 8.0 Hz, 1H), 7.73 (d, J = 15.8 Hz, 1H), 7.58-7.38 (m, 4H), 7.34-7.23 (m, 3H), 7.19-7.11 (m, 3H), 6.98 (s, 1H), 6.25 (d, J = 15.8 Hz, 1H), 2.35 (s, 3H). ^{13}C-NMR: 145.7, 139.0, 137.2, 134.3, 133.6, 133.1, 131.7, 131.0, 129.5 (2C), 128.4, 127.9, 127.7, 127.1 (2C), 124.2, 122.4, 120.0, 119.3, 110.9, 21.3

Table 2. 5-Arylbenzo[*a*]phenazines obtained by benzotriazole ring opening

Entry (Yield)	Product	^{1}H- NMR and ^{13}C-NMR data ($CDCl_3$), δ
6a (81%)		^{1}H-NMR: 9.50 (d, J = 8.0 Hz, 1H), 8.41-8.31 (m, 1H), 8.31-8.21 (m, 1H), 7.98-7.73 (m, 5H), 7.73-7.67 (m, 1H), 7.48 (d, J = 7.5 Hz, 2H), 7.33 (d, J = 7.5 Hz, 2H), 2.48 (s, 3H). ^{13}C-NMR: 146.1, 142.4, 142.3, 141.9, 141.8, 138.1, 136.2, 132.7, 131.2, 130.4, 129.8, 129.7 (2C), 129.5 (2C), 129.2 (2C), 128.3, 127.9, 127.1, 126.1, 125.6, 21.3
6b (65%)		^{1}H-NMR: 9.35 (d, J = 8.2 Hz, 1H), 8.37-8.27 (m, 1H), 8.27-8.18 (m 1H), 7.85 (s, 1H), 7.83-7.75 (m, 2H), 7.68 (s, 1H), 7.58 (d, J = 8.2 Hz, 1H), 7.50 (d, J = 8.0 Hz, 2H), 7.36 (d, J = 8.0 Hz, 2H), 2.49 (s, 3H), 2.48 (s, 3H). ^{13}C-NMR: 145.1, 143.1, 142.9, 142.4, 141.9, 139.8, 137.8, 136.5, 132.9, 129.6 (2C), 129.5 (3C), 129.2 (4C), 129.1, 127.2, 126.8, 125.6, 22.0, 21.3
6c (61%)		^{1}H-NMR: 9.32 (d, J = 8.2 Hz, 1H), 8.33-8.25 (m, 1H), 8.25-8.16 (m, 1H), 7.85-7.72 (m, 3H), 7.66 (s, 1H), 7.56 (d, J = 8.2 Hz, 1H), 7.48 (d, J = 8.3 Hz, 2H), 7.03 (d, J = 8.3 Hz, 2H), 3.86 (s, 3H), 2.46 (s, 3H). ^{13}C-NMR: 159.6, 145.2, 142.5, 142.0, 140.0, 133.0, 131.7, 130.8 (2C), 129.9, 129.6 (2C), 129.3, 129.1, 128.8, 127.0, 126.7, 125.7, 114.0 (2C), 55.4, 22.0 (few signals are overlapped or low intensity)
6d (77%)		^{1}H-NMR: 9.50 (d, J = 8.0 Hz, 1H), 8.12 (s, 1H), 8.01 (s, 1H), 7.92-7.90 (m, 2H), 7.82-7.77 (m, 1H), 7.71-7.66 (m, 1H), 7.63-7.50 (m, 5H), 2.59 (s, 3H), 2.57 (s, 3H). ^{13}C-NMR: 144.3, 142.5, 142.3, 141.7, 141.3, 141.1, 140.8, 139.6, 132.5, 131.6, 129.7, 129.1, 128.5, 128.4, 128.0, 127.8, 127.5, 127.4, 126.8, 125.4, 20.6 (2C).

During the transformation of **4** to **6** the benzotriazole ring formally loses one of its nitrogen atoms. The nearest literature analogies to this transformation are various known[3] phenazine syntheses including the oxidation of *N*-(2-aminoaryl)arylamines and the reduction of *N*-(2-nitroaryl)arylamines. In both cases a

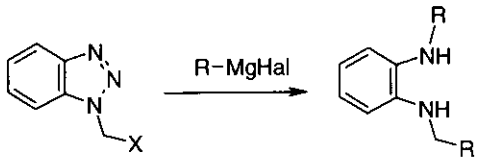
structure with an electrophilic nitrogen functionality is probably an intermediate. By analogy, we believe that the formation of phenazines (**6**) involves an intramolecular electrophilic substitution at the naphthalene ring of cation (**11**) (Scheme 3) followed by the elimination of ammonia. Our hypothesis involves a series of tautomeric rearrangements which convert the initially formed intermediate (**10**) to the more stable aromatic intermediate (**11**) (Scheme 3).



10 **11** **6**

Scheme 3

The extrusion of a single nitrogen atom from a benzotriazole ring during a reaction sequence is rather unusual. However, a few known benzotriazole transformations do involve the cleavage of both the N1-N2 and the N2-N3 bonds. They include some reactions of benzotriazoles of general structure (**12**) with Grignard reagents to form substituted 1,2-phenylenediamines (**13**) (Scheme 4).[4,5] Most of the common heterocyclic ring scissions of benzotriazoles involve cleavage of the N1-N2 bond followed by either ring opening - ring closure, or by elimination of N_2 (for a review see ref. 1, page 536).



12 **13**

X = heteroatom

Scheme 4

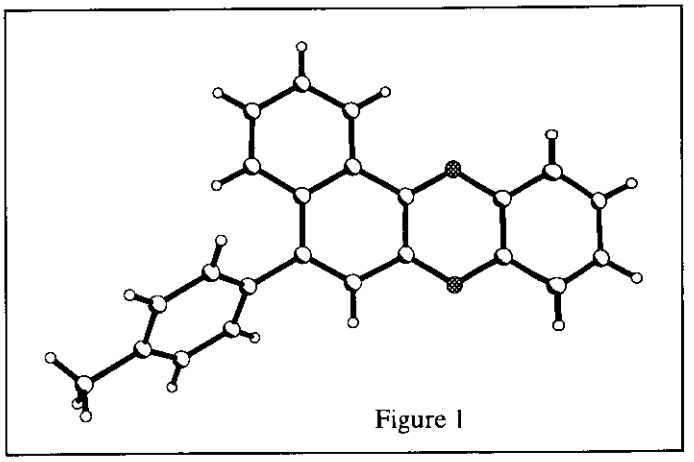


Figure 1

CONCLUSIONS

We have herein described an unusual acid-promoted ring transformation of benzotriazoles to benzo[*a*]phenazines which possesses significant preparative potential.

EXPERIMENTAL

General. Melting points were determined on a Koefler hot stage apparatus and are uncorrected. The ^{1}H and ^{13}C NMR spectra were recorded at 300 MHz and 75 MHz respectively in $CDCl_3$ referenced to Me_4Si for the ^{1}H spectra and $CDCl_3$ for the ^{13}C spectra. Tetrahydrofuran (THF) was distilled under nitrogen from sodium-benzophenone immediately before use. All reactions with moisture-sensitive compounds were carried out under a dry nitrogen atmosphere. 2-(Benzotriazol-1-yl)-1-phenyl-4-(4-methylphenyl)-3-buten-1-ol (**3a**) was prepared according to previously reported procedure.[2] Arylaldehydes (**1**) were used as obtained from commercial sources.

Synthesis of 3-(benzotriazol-1-yl)-1,4-diaryl-1-buten-4-ols (3) and (7); General Procedure. *n*-Butyllithium (3.8 mL, 5.5 mmol, 1.45 M solution in hexanes) was added to a solution of **2** (5 mmol) in THF (40 mL) under argon at -78 °C, and the solution was stirred at this temperature for 1 h. Aldehyde (5 mmol) in THF (10 mL) was added, and the mixture was stirred overnight. The reaction was quenched with a saturated ammonium chloride solution (20 mL). The organic layer was separated, and the aqueous one was extracted with ethyl acetate (3 x 15 mL). The combined organic extracts were dried over magnesium sulfate and filtered. The solvent was evaporated *in vacuo*, and the residue was re-crystallized or chromatographed for analytical purposes using appropriate solvents. Alcohols (**3b-d**) and (**7**) were used for the syntheses of **4** or **6** without further purification.

(E)-2-(1H-1,2,3-Benzotriazol-1-yl)-1,4-bis(4-methylphenyl)-3-buten-1-ol (**3b**): White solid, yield 1.52 g (80% for two diastereomers). ^{13}C-NMR (DMSO-d_6) δ: 144.6, 144.4, 137.4, 137.2, 136.9 (2C), 136.4, 136.1, 133.7, 133.2, 132.5, 132.3, 132.1, 131.9, 128.3 (2C), 128.2 (2C), 128.0, 127.7 (2C), 126.0 (2C), 125.9 (2C), 125.6 (2C), 125.5, 125.4 (4C), 122.8, 122.7, 122.0, 121.9, 118.3, 118.2, 110.3, 110.0, 74.5, 74.3, 67.2, 67.0, 20.1, 20.0.

(E)-2-(1H-1,2,3-Benzotriazol-1-yl)-1-(4-methylphenyl)-4-(4-methoxyphenyl)-3-buten-1-ol (**3c**): White solid, yield 1.45 g (82% for two diastereomers), (major diastereomer, from ether). ^{1}H-NMR (DMSO-d_6) δ: 8.13 (d, J = 8.3 Hz, 1H), 8.04 (d, J = 8.5 Hz, 1H), 7.95 (t, J = 8.2 Hz, 1H), 7.50-7.26 (m, 3H), 7.24 (d, J = 8.5 Hz, 2H), 7.12 (d, J = 7.4 Hz, 2H), 6.84 (d, J = 8.4 Hz, 2H), 6.58 (dd, J = 8.2 Hz, J = 15.6 Hz, 1H), 6.43 (d, J = 15.6 Hz, 1H), 5.85-5.65 (m, 2H), 5.81-5.75 (m, 1H) 3.70 (s, 3H), 2.26 (s, 3H). ^{13}C-NMR (DMSO-d_6) δ: 159.2, 145.2, 139.0, 136.6, 133.6, 133.1, 128.6 (2C), 128.3, 127.7 (2C), 127.1, 126.8, 123.7, 122.3, 118.9, 114.0 (2C), 111.8, 74.6, 67.6, 55.1, 20.7.

(E)-2-(5,6-Dimethyl-1H-1,2,3-benzotriazol-1-yl)-1,4-diphenyl-3-buten-1-ol (**3d**): Oil, one diastereomer was obtained as a yellow oil by column chromatography on silica gel using hexane/EtOAc (3:1) as eluent in 15% yield. ^{1}H-NMR δ: 7.50 (s, 1H), 7.45-7.42 (m, 2H), 7.34-7.00 (m, 9H), 6.42 (dd, J = 7.4 Hz, J = 15.9 Hz, 1H), 6.16 (d, J = 15.9 Hz, 1H), 5.63 (d, J = 7.8 Hz, 1H), 5.52-5.47 (dd, J = 7.4 Hz, J = 7.8 Hz, 1H), 4.71 (s, 1H), 2.35 (s, 3H), 2.28 (s, 3H). ^{13}C-NMR δ: 144.4, 140.2, 137.6, 135.6, 134.1, 133.7, 132.5, 128.4, 128.1, 128.0, 127.8, 126.8, 126.4, 123.9, 118.4, 109.2, 76.0, 67.9, 20.8, 20.2.

Synthesis of 2-(1*H*-benzotriazol-1-yl)-4-aryl-6-*R*-3,4-dihydronaphthalene (4a-c) and diene (8); General Procedure. A mixture of 2 mmols of 3-(benzotriazol-1-yl)-1,4-diaryl-1-buten-4-ol (**3**) and 1 mL of conc. H_2SO_4 in glacial acetic acid (6 mL) was heated at 80 °C for 3 h. The red-brown reaction mixture was cooled to 20 °C and poured onto ice (about 30 g), extracted with ether (3 x 100 mL) and dried over magnesium sulfate. The solvent was evaporated and the residue was crystallized from the minimum amount of ether.

2-(1H-1,2,3-Benzotriazol-1-yl)-4-(4-methylphenyl)-3,4-dihydronaphthalene (**4a**): mp = 146-147 °C. *Anal.* Calcd for $C_{23}H_{19}N_3$: C, 81.83; H, 5.68; N, 12.45. Found: C, 81.46; H, 5.87; N, 12.34.

2-(1H-1,2,3-Benzotriazol-1-yl)-4-(4-methylphenyl)-6-methyl-3,4-dihydronaphthalene (**4b**): mp = 150-151 °C. *Anal.* Calcd for $C_{24}H_{21}N_3$: C, 82.02; H, 6.02; N, 11.96. Found: C, 81.56; H, 6.31; N, 12.00.

2-(1H-1,2,3-Benzotriazol-1-yl)-4-(4-methoxyphenyl)-6-methyl-3,4-dihydronaphthalene (**4c**): mp = 141-143 °C. *Anal.* Calcd for $C_{24}H_{21}N_3O$: C, 78.45; H, 5.76; N, 11.44. Found: C, 78.43; H, 6.21; N, 11.08.

1-(E)-3-(4-Methylphenyl)-1-[2-(thienylmethylidene)-2-propenyl]-1H-1,2.3-benzotriazole (**8**): mp = 137-139 °C. *Anal.* Calcd for $C_{21}H_{17}N_3S$: C, 73.43; H, 5.00; N, 12.24. Found: C, 73.32; H, 5.22; N, 11.64.

Synthesis of 5-arylbenzo[*a*]phenazines (6); General Procedure. A mixture of 2 mmols of 3-(benzotriazol-1-yl)-1,4-diaryl-1-buten-4-ol (**3**) or corresponding 2-(1*H*-benzotriazol-1-yl)-4-aryl-6-*R*-3,4-dihydronaphthalene (**4**) and 1 mL of conc. H_2SO_4 in glacial acetic acid (6 mL) was refluxed for 5 h. The red-brown reaction mixture was cooled to rt and poured into ice (about 30 g). The solid obtained was filtered, washed with water (3 x 5 mL), dissolved in ether and dried over magnesium sulfate. The solvent was evaporated and the residue crystallized from the minimum amount of ether. An analytically pure sample was obtained by sublimation at 150 °C under vacuum 0.2 mm Hg.

5-(4-Methylphenyl)benzo[a]phenazine (**6a**): mp = 188-189 °C. *Anal.* Calcd for $C_{23}H_{16}N_2$: C, 86.21; H, 5.04; N, 8.75. Found: C, 86.29; H, 5.24; N, 8.85.

2-Methyl-5-(4-methylphenyl)benzo[a]phenazine (**6b**): mp = 213-214 °C. *Anal.* Calcd for $C_{24}H_{18}N_2$: C, 86.20; H, 5.43; N, 8.38. Found: C, 86.15; H, 5.54; N, 8.50.

2-Methyl-5-(4-methoxyphenyl)benzo[a]phenazine (**6c**): mp = 196-198 °C. *Anal.* Calcd for $C_{24}H_{18}N_2O$: C, 82.26; H, 5.19; N, 8.00. Found: C, 82.28; H, 5.00; N, 7.97.

8,9-Dimethyl-5-phenylbenzo[a]phenazine (**6d**): mp = 200-202 °C. *Anal.* Calcd for $C_{24}H_{18}N_2$: C, 86.19; H, 5.44; N, 8.38. Found: C, 85.70; H, 5.46; N, 8.34.

X-Ray Crystal Structure of 6a. Data were collected with a Siemens SMART CCD area detector, using graphite monochromatized Mo-Kα radiation (l = 0.71073 Å). The structure was solved by direct methods, and refined on F^2 using all data by full-matrix least-squares procedures. Hydrogen atoms were included in calculated positions with isotropic displacement parameters 1.2 times the isotropic equivalent of their carrier carbons.

Crystal data for **6a** at –118 °C: $C_{23}H_{16}N_2$, M = 320.4, monoclinic, space group $P2_1/c$, a = 13.170(2), b = 19.556(3), c = 6.447(1) Å, b = 101.953(2)°, U = 1624.5(5) $Å^3$, F(000) = 672, Z = 4, D_c = 1.310 g cm^{-3}, m(Mo-Kα) = 0.77 cm^{-1}, $2q_{max}$ = 48°, 227 parameters, S = 1.03, wR2 = 0.113 for all 2551 data, R = 0.045 for 1830 data with $F_o > 4s(F_o)$.

ACKNOWLEDGMENTS

We gratefully acknowledge the financial support of CIES (Fulbright program) for a stipend to ARS Ferwanah.

REFERENCES

1. A. R. Katritzky, X. Lan, I. Z. Yang, and O. V. Denisko, *Chem. Rev.*, 1998, 409.
2. A. R. Katritzky, A. R. S. Ferwanah, and S. N. Denisenko, *Heterocycles*, 1999, **50**, 767.
3. A. E. A. Porter, "Comprehensive Heterocyclic Chemistry", Part 2B, ed. by A. R. Katritzky, C. W. Rees, Pergamon Press, 1984, pp. 157-196.
4. A. R. Katritzky, S. Rachwal, B. Rachwal, *J. Org. Chem.*, 1989, **54**, 6022.
5. A. R. Katritzky, S. Rachwal, B. Rachwal, *J. Chem. Soc., Perkin Trans. 1*, 1990, 1717.

Received, 12th April, 1999