A New Three-Carbon Synthon for Efficient Synthesis of Benzannelated and 1-(2-Arylethenyl) Heterocycles

Alan R. Katritzky,*[,§] Dmytro O. Tymoshenko,[§] Daphne Monteux,[§] Vladimir Vvedensky,[§] George Nikonov,[§] Christopher B. Cooper,[‡] and Milind Deshpande[||]

Center for Heterocyclic Compounds, University of Florida, Department of Chemistry, Gainesville, Florida 32611−7200, Bristol Myers Squibb Co., Pharmaceutical Research Institute, Route 206 & Provinceline Road, Princeton, New Jersey 08563, and Bristol Myers Squibb Co., Pharmaceutical Research Institute, 5 Research Pkwy, Wallingford, Connecticut 06492

katritzky@chem.ufl.edu

Received June 22, 2000

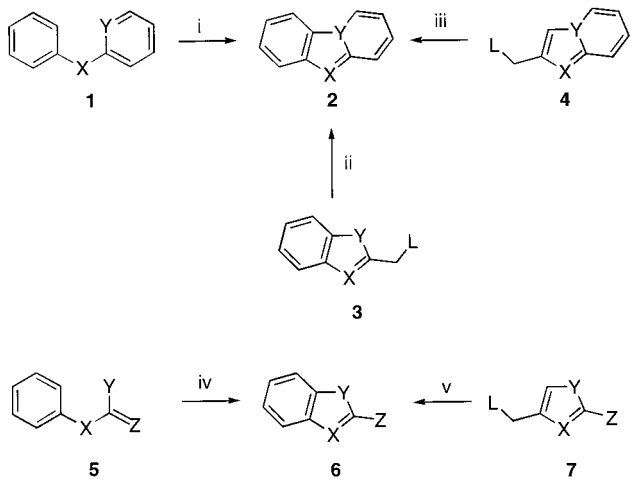
The novel three-carbon synthon 1-(1*H*-1,2,3-benzotriazol-1-yl)-3-chloroacetone for the synthesis of benzothiazoles, pyrido[1,2-*a*]indoles, and styryl-substituted indolizines and imidazo[1,2-*a*]pyridines is reported. The proposed routes are a general and efficient approach for heterocyclizations followed by benzannelations or attachment of arylethenyl pharmacophores.

Introduction

Benzannelation and the introduction of an arylethenyl substituent are efficient methods for the diversification of heterocycles of biological value. Benzo-fused 2-aminothiazoles (methabenzthiazuron, riluzole, sabeluzole, tioxidazole[1]), pyrido[1,2-*a*]benzimidazoles (rifaximin,[1] potential anxiolytics,[2a−2c] antineoplastics,[3] and anticancer agents[4]), and pyrido[1,2-*a*]indoles[5a−5c] demonstrate activities comparable to those of the corresponding nonfused systems. The introduction of arylethenyl substituents has been used widely for the modification of drugs derived from quinoline,[6] pyridinium,[7] thiazole,[8] and thiazolium[9] ring systems. These types of diversification each create systems with additional conjugation and divergent syntheses from single precursors could allow a combinatorial approach.

Most approaches to styryl heterocycles involve reactions of heterocyclic activated methylene substrates with aldehydes or their derivatives.[10,11] This process is facilitated by an activating group in the methylene component.[12,13]

Scheme 1



Classically important methods for the preparation of benzo-fused heterocycles normally involve construction of a heterocycle onto a preformed benzene ring. 6,5,6-Tricyclic type systems (**2**) are usually synthesized using one of two general approaches (i and ii of Scheme 1). Route (i) effects the closure of a five-membered ring in substrates **1**, containing an aryl group attached to a six-membered heteroaromatic ring via carbon (X = CR)[14,15] or nitrogen (X = N).[16,17] This approach involves thermal-[17] or photodehydrocyclization[16] and often affords systems **2** in low yields. Intermediates **1** are usually synthesized starting from *o*-chloronitrobenzenes,[18−20] which narrows the scope for diversification in the fused target systems.

[§] University of Florida.
[‡] Bristol Myers Squibb Co., New Jersey.
[||] Bristol Myers Squibb Co., Connecticut.

(1) *The Merck Index*, 12th ed.; Chapman and Hall: London, 1996; Ver. 12.1.
(2) (a) Maryanoff, B. E.; McComsey, D. F.; Ho, W.; Shank, R. P.; Dubinsky, B. *Bioorg. Med. Chem. Lett.* **1996**, *6*, 333. (b) Cohen, J. H.; Maryanoff, C. A.; Stefanick, S. M.; Sorgi, K. L.; Villani, F. J. *Org. Process Res. Dev.* **1999**, *3*(4), 260. (c) Griebel, G.; Perrault, G.; Tan, S.; Schoemaker, H.; Sanger, D. J. *Behav. Pharmacol.* **1999**, *10*(5), 483.
(3) Badawey, E.; Kappe, T. *Eur. J. Med. Chem.* **1995**, *30*, 327.
(4) El-Hawash, S. A. M.; Badawey, E.; Kappe, T. *Pharmazie* **1999**, *54*, 341.
(5) (a) Taylor, D. L. et al. *Antiviral Chem. Chemother.* **1999**, *10*, 79. (b) Srivastava, S. K. et al. *J. Med. Chem.* **1999**, *42*, 1667. (c) Katsura, Y.; Inoue, Y.; Nishino, S.; Tomoi, M.; Itoh, H.; Takasugi, H. *Chem. Pharm. Bull.* **1992**, *40*(6), 1424.
(6) Rubtsov, M. V.; Pershin, G. N.; Yanbuktin, L. A.; Pelenitsina, L. A.; Gurevich, T. J.; Novitskaya, N. A.; Milovanova, S. N.; Vichkanova, S. A. *J. Med. Pharm. Chem.* **1960**, *2*, 113.
(7) Philips, A. P.; Burrows, R. B. U.S. Patent 3085935, 1963; *Chem. Abstr.* **1963**, *59*, 2598g.
(8) Adelroth, E.; Inman, M. D.; Summers, E.; Pace, D.; Modi, M.; O'Byrne P. M. *J. Allergy Clin. Immunol.* **1997**, *2*, 210.
(9) In *Martindale. The extra Pharmacopoeia*, 28th ed.; Reynolds, J. E. F., Ed.; Pharmaceutical Press: London, 1982; p 1747.
(10) Jayabalan, L.; Shanmugam, P. *Synthesis* **1991**, 217.
(11) Thumel, R. P.; Lefoulon, F.; Cantu, D.; Mahadevan, R. *J. Org. Chem.* **1984**, *49*(12), 2208.
(12) Konakahara, T.; Takagi, Y. *Tetrahedron Lett.* **1980**, *21*(21), 2073.
(13) Konakahara, T.; Takagi, Y. *Heterocycles* **1984**, *22*(12), 2765.
(14) Soldatenkov, A. T.; Bagdadi, M. V.; Fomichev, A. A.; Prostakov, N. S. *Zh. Org. Khim.* **1982**, *18*, 902.
(15) Ohsawa, A.; Kawaguchi, T.; Igeta, H. *Chem. Lett.* **1981**, 1737.
(16) Baklanov, M. V.; Frolov, A. N. *Zh. Org. Khim.* **1991**, *27*, 638.
(17) Prostakov, N. S.; Varlamov, A. V.; Shendrik, I. V.; Anisimiv, B. N.; Krapivko, A. P.; Lavani-Edogiaverie, S.; Fomichev, A. A. *Khim. Geterotsikl. Soedin.* **1983**, 1384.

10.1021/jo000946r CCC: $19.00
Published on Web 10/21/2000

The second route (ii) represents heteroring annelation of intermediates **3** bearing a leaving group L, with three carbon dielectrophiles (e.g., 1,3-diketones[21,22] or propargyl bromide[23]). This provides systems **2** in 10−40% yields, but gives regioisomer mixtures at the intermediate step.[23]

Type 5,6-fused bicycles **6** have previously been prepared by pathway (iv) from **5** via photodehydrocyclization[24] or thermal[25] dehydrocyclization, which gives moderate to good yields of 5,6 systems **6**, but frequently only as the major component of complex mixtures.

To the best of our knowledge, the approaches shown in synthetic routes (iii) and (v) were not previously applied to systems of types **2** and **6**. Pathways (iii) and (v) require intermediates **4** and **7**, respectively. Compounds **4** and **7** could also be used for the introduction of styryl substituents and are, thus, of interest as multipurpose precursors.

Our recent studies of the application of benzotriazoloalkyl(hetero)aromatics as benzoannelation precursors in alternative approaches to benzo-fused five-membered heterocycles have provided versatile new synthesis of benzo[*b*]furans,[26] benzo[*b*]thiophenes,[27] and 5,6-dihydro-4*H*-pyrrolo[3,2,1-*ij*]quinolines.[28] In these transformations, carbanions of the starting benzotriazolylmethyl-heterocycles (easily prepared from the corresponding five-membered heteroaromatics) undergo Michael-type addition to α,*β*-unsaturated ketones and subsequent ring closure. Benzotriazolylmethyl heterocycles are also convenient precursors of styryl heteroaromatics.[27]

We now present an efficient two-step method for the preparation of 5,6- and 6,5,6-fused, and styryl-substituted, heteroaromatic systems based on common precursors which should allow combinatorial approaches to their synthesis. The new three-carbon synthon 1-(1*H*-1,2,3-benzotriazol-1-yl)-3-chloroacetone (**11**) acts as a 1,2-dielectrophile in the first step of [2 + 3]-type heterocyclizations to give **13**, **14**, and **15** (Scheme 2). In these intermediates, the benzotriazoloalkyl(hetero)aromatic structure intermediate reacts either as a 1,3-dinucleophilic moiety for the benzannelation step (to give **16**, **17**) or as a benzotriazole activated methylene intermediate to give heteroaromatic styryl systems **18** and **19**.

Intermediate **11** was prepared in 84% yield by heating neat chloroacetyl chloride with trimethylsilylmethylbenzotriazole **10** (cf. ref 29). Further reaction of **11** with thioureas **12a**, 2-alkylpyridines **12b**, and 2-aminopyridines **12c** as dinucleophiles led to novel benzotriazolylmethyl compounds **13a**−**h**, **14a**−**e,** and **15a**−**f**. 4-(Benzotriazolylmethyl)-2-aminothiazoles **13** were obtained in good to excellent yields (Table 1). When thiourea was reacted with **11** in DMF instead of ethanol only *N*-[4-(1*H*-1,2,3-benzotriazol-1-ylmethyl)-1,3-thiazol-2-yl]formamide was isolated in 54% yield. In the case of 2-(benzotriazolylmethyl)-indolizines **14** (Table 2), this transformation demanded harsher conditions (refluxing DMF instead of ethanol for **13** and **15**), and the reactivity of substituted 2-alkylpyridines depended on the position of the substituent in the starting pyridine. Thus, almost quantitative conversion of the starting material was achieved in 4, 0.5 and 0.75 h during the preparation of compounds **14b**−**d**, correspondingly. Benzotriazolyl-substituted indolizines **14a**−**d** were prepared in 54−66% yields, while the yield of **14e** was 32%. No reaction was observed in the case of 2,6-dimethylpyridine. The yields of 1-(imidazo[1,2-*a*]pyridin-2-ylmethyl)-1*H*-1,2,3-benzotriazoles **15a**−**f** were 49−76% (Table 3).

Scheme 2

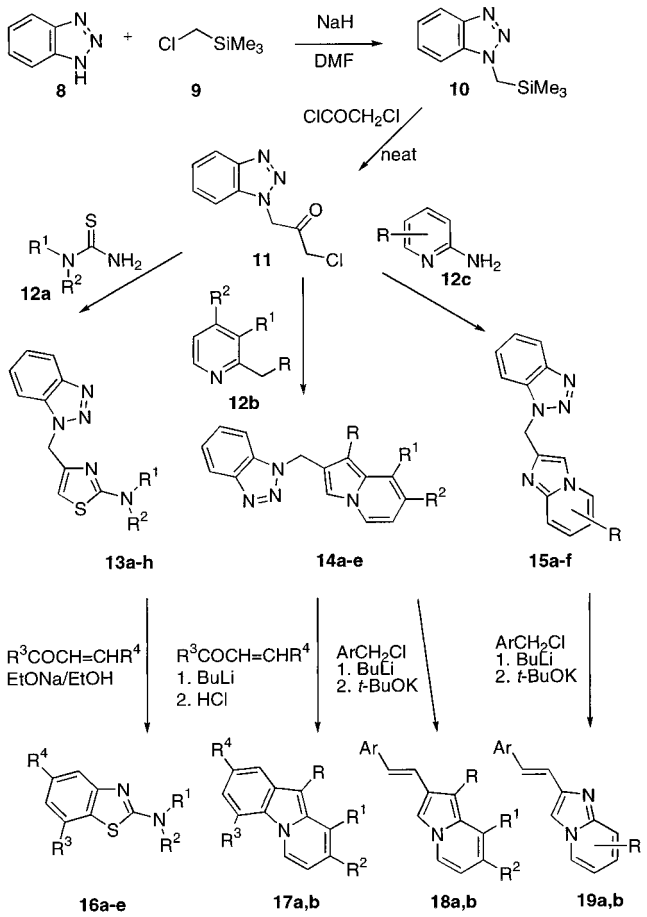


Table 1. 4-Benzotriazolylmethyl 2-Aminothiazoles 13

entry	R^1	R^2	yield, %
a	H	H	59
b	Ph	H	82
c	4-Cl-C_6H_4	H	77
d	Ph	Ph	86
e	4-NO_2-C_6H_4	H	69
f	2-Cl-C_6H_4	H	77
g	4-CH_3O-C_6H_4	H	65
h	1-naphthyl	H	81

Table 2. 2-Benzotriazolylmethyl Indolizines 14

entry	R	R^1	R^2	yield, %
a	H	H	H	62
b	H	H	Me	66
c	H	Me	H	64
d	Me	H	H	54
e		$(CH_2)_3$	H	32

(18) Anderson, D. J.; Taylor, A. J. *J. Heterocycl. Chem.* **1986**, *23*, 1091.
(19) Morgan, G. T.; Stewart, J. *Chem. Ind.* **1937**, 670.
(20) Stephenson, L.; Warburton, W. K. *J. Chem. Soc. C* **1970**, 1355.
(21) Popov, I. I. *Khim. Geterotsikl. Soedin.* **1989**, 1695.
(22) Kuz'menko, V. V.; Komissarov, V. N.; Simonov, A. M. *Khim. Geterotsikl. Soedin.* **1981**, 1497.
(23) Bergerat, I.; Galons, H.; Rabaron, A.; Combet-Farnoux, C.; Miocque, M. *J. Heterocycl. Chem.* **1985**, *22*, 369.
(24) Muthusamy, S.; Paramasivam, R.; Ramakrishnan, V. T. *J. Heterocycl. Chem.* **1991**, *28*, 759.
(25) Tweit, R. C. *J. Heterocycl. Chem.* **1970**, 687.
(26) Katritzky, A. R.; Fali, C. N.; Li, J. *J. Org. Chem.* **1997**, *62*, 8205.
(27) Katritzky, A. R.; Serdyuk, L.; Xie, L.; Ghiviriga, I. *J. Org. Chem.* **1997**, *62*, 6215.
(28) Katritzky, A. R.; Fali, C. N.; Li, J. *J. Org. Chem.* **1997**, *62*, 4148.
(29) Katritzky, A. R.; Lam, J. N. *Heteroatom Chem.* **1990**, *1*, 21.

Table 3. 1-(Imidazo[1,2-*a*]pyridin-2-ylmethyl)-1*H*-1,2,3-benzotriazoles 15

entry	substituents	yield, %
a	H	55
b	7-Me	49
c	8-CH_3	50
d	5,7-$(CH_3)_2$	43
e	8-$OCH_2C_6H_5$	76
f	6-Cl	50

Table 4. 5,7-Disubstituted 2-Aminobenzothiazoles 16

entry	R^1	R^2	yield, %
a	Ph	Ph	74
b	4-CH_3-C_6H_4	4-CH_3O-C_6H_4	63
c	Ph	4-NO_2-C_6H_4	59
d	Ph	4-Cl-C_6H_4	72
e	H	Ph	25

The structure of compounds **13**−**15** was confirmed by ^{1}H and ^{13}C NMR spectra.

Reaction of **13** with chalcones in ethanol in the presence of sodium ethoxide led to benzothiazoles **16a**−**d** in good yields (Table 4, Scheme 2). Reaction with cinnamic aldehyde (R^1 = H, R^2 = Ph), which is prone to side reactions in strong basic media, gave the desired *N*,5-diphenyl-1,3-benzothiazole-2-amine (**16e**) in 25% yield. We further extended this result to the synthesis of pyrido[1,2-*a*]indoles **17a**,**b** in 54% and 57% yields. Intermediates **14** demanded generation of carbanion by treatment with BuLi and sequential cyclization of a Michael-type product generated in situ and indicated by TLC under acidic conditions. Intermediate **14c** was further reacted with (chloromethyl)arenes to afford 2-styryl indolizines **18a** and **18b** in 70 and 75% yields, correspondingly. This sequence was further extended to the preparation of 2-(2-arylethenyl)imidazo[1,2-*a*]pyridines **19a**,**b** which were prepared in 71−75% yields.

Conclusion

A general and efficient approach to unified precursors for the preparation of benzo-fused and styryl-substituted heteroaromatic systems was developed. Such an approach is based on the novel three-carbon synthon 1-(1*H*-1,2,3-benzotriazol-1-yl)-3-chloroacetone which resulted in high yields of benzothiazoles **16**, pyrido[1,2-*a*]indoles **17** and styryl-substituted indolizines **18** and imidazo[1,2-a]-pyridines **19**. The proposed routes open special opportunities for heterocyclizations followed by benzannelations or attachment of arylethenyl pharmacophores.

Experimental Section

(Trimethylsilylmethyl)benzotriazole **10** was synthesized according to the already reported procedure.[29]

Preparation of 1-(1*H*-1,2,3-Benzotriazol-1-yl)-3-chloropropan-2-one (11). 1-[(Trimethylsilyl)methyl]-1*H*-1,2,3-benzotriazole (**10**) (2.05 g, 0.01 mol) was dissolved in chloroacetyl chloride (0.8 mL, 0.01 mol) at room temperature. After 10−20 s, the evolution of chlorotrimethylsilane was observed and the mixture began to solidify. The solid obtained was triturated with ether, filtered off, and washed with ether to afford an analytically pure sample as pale yellow needles: mp 159.0 °C (84%); ^{1}H NMR δ 4.72 (s, 2H), 5.86 (s, 2H), 7.30 (t, J = 7.5 Hz, 1 H), 7.44 (t, J = 7.5 Hz, 1 H), 7.65 (d, J = 8.1 Hz, 1 H), 7.95 (d, J = 8.1 Hz, 1 H); ^{13}C NMR δ 47.1, 54.3, 110.7, 119.1, 124.0, 127.4, 133.6, 145.0, 195.6. Anal. Calcd for $C_9H_8ClN_3O$: C, 51.56; H, 3.85; N, 20.05. Found: C, 51.68; H, 3.65; N, 20.01.

General Procedure for the Preparation of 2-Amino-(4-benzotriazolylmethyl)thiazoles 13. 1-(1*H*-1,2,3-Benzotriazol-1-yl)-3-chloropropan-2-one (**11**) (10 mmol) and the corresponding thiourea (10 mmol) were stirred in EtOH (20 mL) under reflux for 12 h. After completion of the reaction (TLC, hexanes/EtOAc = 1:2), the reaction mixture was deluted with water (20 mL), and the precipitate was filtered off and recrystallized from methanol.

4-(1*H*-1,2,3-Benzotriazol-1-ylmethyl)-1,3-thiazol-2-ylamine (13a): white microprisms; yield 59%; mp 189.0−192.0 °C; ^{1}H NMR δ 5.96 (s, 2H), 6.52 (s, 1H), 6.86 (s, 2H), 7.35 (t, J = 7.5 Hz, 1H), 7.47 (t, J = 7.5 Hz, 1H), 7.73 (d, J = 8.4 Hz, 1H), 7.96 (d, J = 8.4 Hz, 1H); ^{13}C NMR δ 46.4, 102.9, 109.1, 117.3, 121.9, 125.2, 131.1, 143.7, 143.8, 167.6. Anal. Calcd for $C_{10}H_9N_5S$: C, 51.93; H, 3.93. Found: C, 51.64; H, 4.07.

***N*-[4-(1*H*-1,2,3-Benzotriazol-1-ylmethyl)-1,3-thiazol-2-yl]-*N*-phenylamine (13b):** white microprisms; yield 82%; mp 168.0 °C; ^{1}H NMR δ 5.78 (s, 2H), 6.78 (t, J = 7.5 Hz, 1H), 6.82 (s, 1H), 7.09 (t, J = 7.2 Hz, 2H), 7.27−7.35 (m, 3H), 7.47 (t, J = 7.5 Hz, 1H), 7.86 (d, J = 8.4 Hz, 1H), 7.93 (d, J = 8.1 Hz, 1H), 10.10 (s, 1H); ^{13}C NMR δ 47.7, 106.2, 111.4, 116.8, 119.1, 121.3, 123.9, 127.1, 128.8, 133.1, 140.9, 145.3, 146.0, 163.9. Anal. Calcd for $C_{16}H_{13}N_5S$: C, 62.52; H, 4.27; N, 22.79. Found: C, 62.21; H, 4.24; N, 22.69.

General Procedure for the Preparation of 1-(2-Indolizinylmethyl)-1*H*-1,2,3-benzotriazoles 14. 1-(1*H*-1,2,3-benzotriazol-1-yl)-3-chloropropan-2-one (**11**) (2 mmol) and the corresponding 2-alkylpyridines (4 mmol) were stirred in DMF (15 mL) under reflux for 40 min. The completion of the reaction was monitored by TLC (hexanes/EtOAc = 1:1). The reaction mixture was diluted with ether (40 mL) and washed with water (6 × 10 mL). Combined water layers were extracted with ether (20 mL). Organic extracts were dried ($MgSO_4$), concentrated in vacuo, and purified column chromatography (silica gel, ethyl acetate/hexane = 1:1) to give pure products.

1-(2-Indolizinylmethyl)-1*H*-1,2,3-benzotriazole (14a): white plates; yield 62%; mp 150.0 °C; ^{1}H NMR δ 5.94 (s, 2H), 6.35 (s, 1H), 6.43 (t, J = 6.4 Hz, 1H), 6.62 (dd, J = 6.5 Hz, 9.0 Hz, 1H), 7.25 (d, J = 8.7 Hz, 2H), 7.29−7.49 (m, 3H), 7.78 (d, J = 6.8 Hz, 1H), 8.05 (d, J = 8.1 Hz, 1H); ^{13}C NMR δ 46.0, 98.4, 109.9, 110.7, 111.0, 117.7, 119.0, 119.9, 122.7, 123.7, 125.0, 127.1, 132.7, 133.1, 146.2. Anal. Calcd for $C_{15}H_{12}N_4$: C, 72.56; H, 4.88; N, 22.57. Found: C, 72.27; H, 4.94; N, 22.43.

1-[(7-Methyl-2-indolizinyl)methyl]-1*H*-1,2,3-benzotriazole (14b): white plates; yield 66%; mp 162.0 °C; ^{1}H NMR δ 2.21 (s, 3H), 5.91 (s, 2H), 6.20 (s, 1H), 6.37 (d, J = 7.0 Hz, 1H), 7.00 (s, 1H), 7.15 (s, 1H), 7.26−7.47 (m, 3H), 7.68 (d, J = 7.2 Hz, 1H), 8.05 (d, J = 8.0, 1H); ^{13}C NMR δ 21.0, 46.1, 96.9, 110.0, 110.3, 113.5, 117.0, 120.0, 122.7, 123.7, 124.6, 127.0, 127.9, 132.7, 133.5, 146.3. Anal. Calcd for $C_{16}H_{14}N_4$: C, 73.25; H, 5.39; N, 21.36. Found: C, 73.20; H, 5.48; N, 21.36.

General Procedure for the Preparation of 1-(Imidazo-[1,2-*a*]pyridin-2-ylmethyl)-1*H*-1,2,3-benzotriazoles 15. 1-(1*H*-1,2,3-Benzotriazol-1-yl)-3-chloropropan-2-one (**11**) (10 mmol) and the corresponding 2-aminopyridines (10 mmol) were stirred in EtOH (10 mL) under reflux for 12 h. After completion of the reaction (TLC, hexanes/EtOAc = 1:2), the reaction mixture was evaporated under reduced pressure. The crude mixture was then washed with water (10 mL) and extracted with CH_2Cl_2 (2 × 10 mL). The organic layer was dried ($MgSO_4$) and concentrated under reduced pressure to give the crude product, which was further purified by neutral alumina column chromatography (hexanes/EtOAc = 1:2) to give pure products.

1-(Imidazo[1,2-*a*]pyridin-2-ylmethyl)-1*H*-1,2,3-benzotriazole (15a): white microprisms; yield 55%; mp 173.0−174.0 °C; ^{1}H NMR δ 6.04 (s, 2H), 6.77 (dd, J = 6.7 Hz, 6.8 Hz, 1H), 7.18 (dd, J = 7.3 Hz, 8.5 Hz, 1H), 7.33−7.37 (m, 2H), 7.45 (dd, J = 7.1 Hz, 7.9 Hz, 1H), 7.58 (d, J = 9.2 Hz, 1H), 7.68 (d, J = 8.2 Hz, 1H), 7.99 (d, J = 6.7 Hz, 1H), 8.06 (d, J = 8.4 Hz, 1H); ^{13}C NMR δ 46.8, 110.1, 110.5, 112.5, 117.4, 119.6, 123.8, 125.0, 125.7, 127.2, 132.8, 140.9, 145.0, 146.0. Anal. Calcd for $C_{14}H_{11}N_5$: C, 67.45; H, 4.46. Found: C, 67.26; H, 4.73.

1-[(7-Methylimidazo[1,2-*a*]pyridin-2-yl)methyl]-1*H*-1,2,3-benzotriazole (15b): white microprisms; yield 49%; mp

156.0−157.0 °C; ^{1}H NMR δ 2.36 (s, 3H), 6.00 (s, 2H), 6.59 (d, J = 6.9 Hz, 1H), 7.28 (s, 1H), 7.31−7.37 (m, 2H), 7.43 (dd, J = 7.3 Hz, 7.7 Hz, 1H), 7.67 (d, J = 8.2 Hz, 1H), 7.85 (d, J = 6.8 Hz, 1H), 8.05 (d, J = 8.3 Hz, 1H); ^{13}C NMR δ 21.3, 47.0, 109.9, 110.2, 115.3, 115.8, 119.7, 123.8, 124.9, 127.3, 132.9, 136.1, 140.7, 145.6, 146.1. Anal. Calcd for $C_{15}H_{13}N_5$: C, 68.42; H, 4.99. Found: C, 68.42; H, 5.39.

General Procedure for the Preparation of Benzothiazole-2-amines 16. 4-Benzotriazolylmethyl 2-aminothiazole **13** (10 mmol) and the corresponding chalcone (10 mmol) were stirred in the solution of sodium (0.23 g, 10 mmol) in EtOH (30 mL) under reflux for 12 h. After completion of the reaction (TLC, hexanes/EtOAc = 1:4), the reaction mixture was evaporated under reduced pressure. The mixture was then diluted with water (10 mL), and the product filtered off and recrystallized from acetone/methanol mixture to give pure products.

***N*,5,7-Triphenyl-1,3-benzothiazol-2-amine (16a):** white microprisms; yield 74%; mp 215.0 °C; ^{1}H NMR δ 7.02 (t, J = 7.5 Hz, 1H), 7.31−7.37 (m, 3H), 7.41−7.53 (m, 5H), 7.69−7.72 (m, 4H), 7.76−7.84 (m, 4H), 10.16 (br s, 1H); ^{13}C NMR δ 115.6, 117.1, 119.9, 121.1, 125.8, 126.1, 126.3, 126.8, 127.4, 127.6, 127.7, 134.1, 138.3, 139.4, 139.5, 139.6, 152.6, 161.5. Anal. Calcd for $C_{25}H_{18}N_2S$: N, 7.40. Found: N, 7.24.

5-(4-Methoxyphenyl)-7-(4-methylphenyl)-*N*-phenyl-1,3-benzothiazol-2-amine (16b): white microprisms; yield 63%; mp 205.0 °C; ^{1}H NMR δ 2.42 (s, 3H), 3.83 (s, 3H), 7.01 (t, J = 7.6 Hz, 1H), 7.31−7.37 (m, 3H), 7.41−7.53 (m, 5H), 7.69 (d, J = 6.5 Hz, 2H), 7.76−7.84 (m, 4H), 10.17 (bs, 1H); ^{13}C NMR δ 22.6, 41.7, 113.1, 114.3, 117.8, 118.6, 121.9, 123.6, 123.8, 124.7, 127.8, 131.8, 135.9, 137.6, 137.7, 142.2, 145.3, 150.5, 154.2, 158.8, 162.1. Anal. Calcd for $C_{27}H_{22}N_2OS$: N, 6.63. Found: N, 6.68.

General Procedure for the Preparation of 4,2-Disubstituted Pyrido[1,2-*a*]indoles 17. 1-(2-Indolizinylmethyl)-1*H*-1,2,3-benzotriazole **14** (1 mmol) was dissolved in 25 mL of dry THF under Ar and cooled to −78 °C, and *n*-BuLi (1 mmol, 0.66 mL, 1.5 N solution in hexanes) was added dropwise. A deep-blue solution formed was kept at −78 °C for 2 h, and then the solution of chalcone (1 mmol) in 3 mL of dry THF was added. The reaction mixture was allowed to warm to room temperature over 12 h and monitored by TLC (hexanes/EtOAc = 25:1). After removal of the solvent the residue was dissolved in 20 mL of 17% HCl and refluxed 4 h. The mixture was neutralized with ammonia and extracted with ether (3 × 20 mL). Crude material obtained after removal of ether was purified on column (silica gel, hexanes/EtOAc = 25:1) to give pure product.

9-Methyl-4-(4-methylphenyl)-2-phenylpyrido[1,2-*a*]indole (17a): white microprisms; yield 54%; mp 147.0 °C; ^{1}H NMR δ 2.45 (s, 3H), 2.48 (s, 3H), 6.09 (t, J = 6.8 Hz, 1H), 6.61 (d, J = 6.2, 1H), 6.74 (br s, 1H), 7.30−7.35 (m, 4H), 7.39−7.47 (m, 4H), 7.62 (d, J = 7.2 Hz, 1H), 7.72 (d, J = 7.2, 2H), 8.00 (d, J = 1.6 Hz, 1H); ^{13}C NMR δ 18.6, 21.3, 91.1, 107.3, 117.6, 120.3, 122.3, 124.8, 126.7, 126.8, 127.5, 127.7, 128.6, 128.8, 129.3, 129.4, 130.4, 135.3, 136.9, 137.5, 138.9, 141.9. Anal. Calcd. for $C_{26}H_{21}N$: N, 4.03. Found: N, 3.87.

9-Methyl-2-(4-methylphenyl)-4-(2-thienyl)pyrido[1,2-*a*]indole (17b): white plates; yield 57%; mp 112.0 °C; ^{1}H NMR δ 2.43 (s, 3H), 2.48 (s, 3H), 6.08 (t, J = 6.8 Hz, 1H), 6.59 (d, J = 6.5 Hz, 1H), 6.70 (s, 1H), 7.07 (dd, J = 3.7, 5.1 Hz, 1H), 7.24 (dd, J = 5.1, 1.0 Hz, 1H), 7.30−7.42 (m, 6H), 7.56 (d, J = 7.3 Hz, 1H), 8.02 (d, J = 1.7 Hz, 1H); ^{13}C NMR δ 18.58, 21.35, 91.1, 107.4, 116.4, 120.4, 121.2, 122.6, 124.2, 124.6, 126.8, 127.7, 127.9, 128.6, 129.0, 129.3, 129.4, 130.3, 136.6, 137.6, 139.0, 145.5. Anal. Calcd for $C_{24}H_{19}NS$: N, 3.96. Found: N, 3.65.

General Procedure for the Preparation of 2-[(*E*)-2-Arylethenyl]indolizines 18 and 2-(2-Phenylethenyl)imidazo[1,2-*a*]pyridines 19. *n*-BuLi (1 mmol, 0.66 mL of 1.5 N solution in hexanes) was added dropwise to the solution of indolizine **14c** (0.262 g, 1 mmol) or imidazo[1,2-*a*]pyridine **15a** in dry THF (25 mL) under Ar at −78 °C. A deep-blue solution formed and was kept at −78 °C for 2 h, and then benzyl chloride (0.127 g, 1 mmol) was added. The reaction mixture was allowed to warm to room temperature during 12 h and monitored by TLC (hexanes/EtOAc = 4:1). Then, *t*-BuOH (10 mL) and *t*-BuOK (1 g) were added, and the mixture was refluxed for 72 h. The residue that formed after removal of solvents was treated with water (15 mL) and extracted with ether (3 × 10 mL). Crude material obtained after removal of ether was recrystallized from ethanol to give pure product.

8-Methyl-2-[(*E*)-2-phenylethenyl]indolizine (18a): white microprisms; yield 75%; mp 138.0 °C; ^{1}H NMR δ 2.40 (s, 3H), 6.36 (t, J = 6.7 Hz, 1 H), 6.44 (d, J = 6.5, 1H), 6.58 (s, 1H), 7.03 (d, J = 16.2 Hz, 1H), 7.16 (d, J = 16.2 Hz, 1H), 7.20−7.25 (m, 1H), 7.30−7.39 (m, 3H), 7.47−7.52 (m, 2H), 7.71 (d, J = 6.7, 1H); ^{13}C NMR δ 18.1, 94.5, 110.4, 112.0, 116.7, 122.1, 122.9, 126.0, 126.6, 126.9, 127.5, 127.8, 128.5, 134.6, 137.8. Anal. Calcd for $C_{17}H_{15}N$: N, 6.00. Found: N, 6.14.

8-Methyl-2-[(*E*)-2-(1-naphthyl)ethenyl]indolizine (18b): white microprisms; yield 70%; mp 109.0 °C; ^{1}H NMR δ 2.42 (s, 3H), 6.37 (t, J = 6.7 Hz, 1H), 6.46 (d, J = 6.6 Hz, 1H), 6.68 (s, 1H), 7.22 (s, 1H), 7.41−7.56 (m, 4H), 7.70−7.88 (m, 5H), 8.28 (d, J = 7.8 Hz, 1H); ^{13}C NMR δ 18.2, 94.6, 110.5, 112.1, 112.2, 116.8, 122.9, 123.0, 123.9, 124.4, 125.0, 125.7, 125.8, 127.0, 127.7, 127.9, 128.5, 131.2, 133.7, 134.7,135.4. Anal. Calcd for $C_{21}H_{17}N$: N, 4.94. Found: N, 4.99.

2-[(*E*)2-Phenylethenyl]imidazo[1,2-*a*]pyridine (19a): white microprisms; yield 71%; mp 160.0 °C; ^{1}H NMR δ 6.75 (t, J = 6.8 Hz, 1H), 7.11−7.20 (m, 2H), 7.24−7.28 (m, 2H), 7.34−7.39 (m, 2H), 7.52−7.62 (m, 4H), 8.06 (d, J = 7.2 Hz, 1H); ^{13}C NMR δ 110.9, 112.5, 117.5, 120.2, 125.3, 125.7, 126.9, 127.0, 128.0, 128.9, 130.8, 137.5, 144.5, 146.0. Anal. Calcd for $C_{15}H_{12}N_2$: N, 12.72. Found: N, 12.68.

2-[(*E*)-2-(4-Chlorophenyl)ethenyl]imidazo[1,2-*a*]pyridine (19b): white microprisms; yield 74%; mp 225.0 °C; ^{1}H NMR δ 6.75 (dt, J = 1.0, 6.3 Hz, 1H), 7.08−7.20 (m, 2H), 7.30−7.34 (m, 2H), 7.44−7.48 (m, 3H), 7.53−7.58 (m, 2H), 8.05 (dt, J = 1.0, 6.6 Hz, 1H); ^{13}C NMR δ 111.3,112.5, 112.7, 117.7, 120.9, 125.6, 125.9, 128.2, 129.3, 129.6, 136.2, 144.2, 146.2. Anal. Calcd for $C_{15}H_{11}ClN_2$: C, 70.72; H, 4.36; N, 11.00. Found: C, 70.79; H, 4.36; N, 11.05.

Supporting Information Available: ^{1}H, ^{13}C, and CHN analysis data for compounds **13c**−**h**, **14c**−**e**, **15c**−**f**, and **16c**−**e**. This material is available free of charge via the Internet at http://pubs.acs.org.

JO000946R