Benzotriazole-Assisted Preparations of 2-(Substituted amino)pyridines and Pyrid-2-ones

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Base-promoted reactions of benzotriazolyl-containing acetic acid derivatives, 2-(benzotriazol-1-yl)acetonitrile (**7a**), 2-(benzotriazol-1-yl)acetamide (**7b**), and (±)-2-(benzotriazol-1-yl)propionamide (**7c**), with α,*β*-unsaturated ketones **8** give efficient and regioselective access to previously difficult to attain *3-unsubstituted* pyridine derivatives: the 2-(substituted amino)pyridines **14a**−**k** and the 4,6-substituted pyrid-2-ones **15a**−**h**. The pyridine rings result from tandem [3 + 3] annulations involving a Michael addition followed by cyclization.

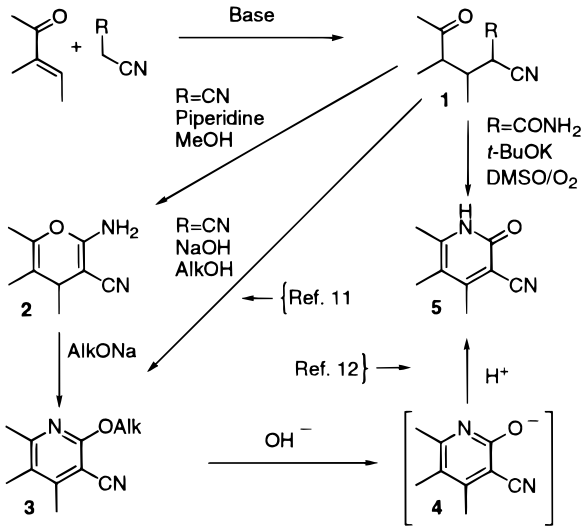
Introduction

2-(Substituted amino)pyridines were previously mostly prepared (i) by reaction of primary or secondary aliphatic amines with 2-halopyridines[1−5] or with imidol silyl ethers derived from the corresponding pyrid-2-ones,[6] (ii) by aminolysis of 2-alkoxypyridines,[3] and (iii) by pyridine ring formation reactions, usually of the [4 + 2] or [3 + 3] type.[7,8] Of these methods, pathway i is the most concise and efficient but requires high temperatures and pressure.[1,3,5] Method ii found application only for alkoxypyridines containing activating groups in the pyridine ring.[3] Ring formation reactions iii in the aminopyridine series are quite rare and have found limited application.[8] A previous report from our laboratory disclosed efficient *N*-alkylations of 2-aminopyridines, achieved by $NaBH_4$ reduction of the adducts formed from benzotriazole, aldehydes, and 2-aminopyridines.[9]

Many syntheses of pyridones[7,8] involve a CCN fragment of cyanoacetamide or malononitrile in a [3 + 3] annulation reaction, thus leaving a cyano group in the C(3)-position of the pyridone system.[8] Such reactions are regioselective and involve a Michael addition of a malonic acid derivative to an α,*β*-unsaturated carbonyl compound, followed by cyclization and aromatization of an intermediate dihydropyridone. Syntheses of *C(3)-unsubstituted* pyridones are less common: recently, Barluenga *et al.* utilized the ring closure of acylated aminoazabutadienes in the presence of LDA.[10]

We now report that reactions of α,*β*-unsaturated ketones with 2-(benzotriazol-1-yl)acetonitrile and *sec*-amines in ethanol readily afford the corresponding 2-(substituted amino)pyridines. Furthermore, 2-(benzotriazol-1-yl)acetamide and (±)-2-(benzotriazol-1-yl)propionamide under similar conditions, but in the presence of NaOH, smoothly form the corresponding substituted pyrid-2-ones.

Scheme 1



Previously, the reaction of α,*β*-unsaturated carbonyl compounds and malononitrile in the presence of piperidine as a base was shown[11] to give 2-amino-3-cyano-2*H*-pyrans **2** as major reaction products (Scheme 1), whereas when NaOH was used as a base, 2-alkoxy-3-cyanopyridines **3** were isolated directly. Pyrans **2** were subsequently converted into 2-alkoxypyridines **3** by sodium alkoxides. Recently, Ciufolini and co-workers prepared substituted 3-cyanopyrid-2-ones **5** from various enones and enals with cyanoacetamide in DMSO using *t*-BuOK as a base under an oxygen atmosphere.[12] Their proposed mechanism involves a molecule of oxygen in the single electron transfer (SET) process, thus enabling the aromatization of the ring.

We reasoned that 2-alkoxypyridines **3** were probably the key intermediates in both pathways utilizing either malononitrile or cyanoacetamide. Thus, the formation

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Scheme 2

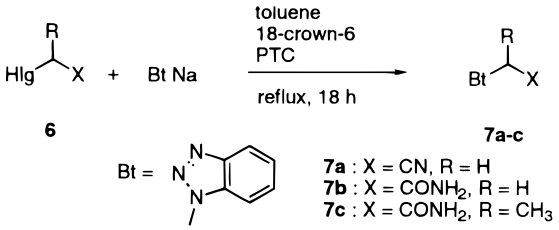


Table 1. Preparation of Benzotriazole-Substituted CH-Active Intermediates 7

compd 7	R	X	yield, %	mp, °C (solvt)	molecular formula	elemental analysis, found (required) C	H	N
a	H	CN	72	87−88 (85−86)[a] (benzene)	$C_8H_6N_4$			
b	H	$CONH_2$	81	163−164 (EtOAc)	$C_8H_8N_4O$	54.85 (54.54)	4.51 (4.58)	31.68 (31.80)
c	Me	$CONH_2$	67	142 (MeOH)	$C_9H_{10}N_4O$	56.65 (56.83)	5.30 (5.30)	29.42 (29.46)

[a] Lit.[14] mp.

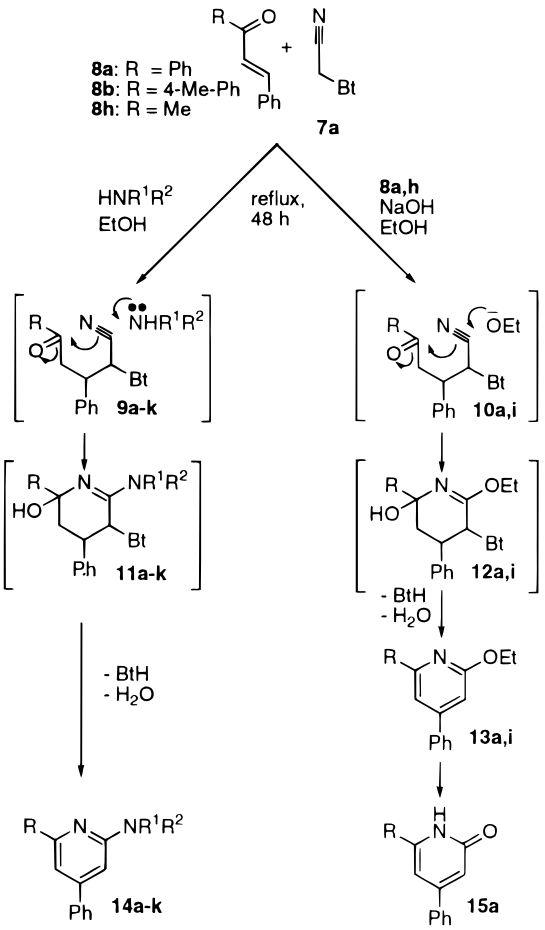
of pyran system **2** is followed by "base-catalyzed ring opening and recyclization" to form 2-alkoxypyridines **3**," [11] by analogy with pyrylium/pyridinium conversion.[13] Although transformation of pyridines **3** into pyridones **5** was not yet established, Ciufolini *et al.*[12] proposed that malonamic ester $EtOOCCH_2CONH_2$ reacts with 1-(1-propyl)-3-(quinolin-2-yl)prop-1-en-3-one in DMSO/*t*-BuOK with the formation of an intermediate anion whose structure was similar to **4** (Scheme 1). The presence of a labile benzotriazole moiety in place of the cyano group in structure **1** should facilitate the formation of the adjacent double bond and thus facilitate the formation of either pyridine **3** or pyridone **5**.

Results and Discussion

We employed a new method for the preparations of previously described 2-(benzotriazol-1-yl)acetonitrile (**7a**) and 2-(benzotriazol-1-yl)acetamide (**7b**) and also of the new (±)-2-(benzo-triazol-1-yl)propionamide (**7c**). Compound **7a** was previously synthesized by reaction of 1-(chloromethyl)benzotriazole with sodium cyanide in DMSO for 3 days[14] and was subsequently converted into **7b** by treatment with H_2O_2 in DMSO.[15] We prepared compounds **7a**−**c** in good yields by reaction of sodium benzotriazolate with the corresponding halides **6a**−**c** in refluxing toluene in the presence of a phase-transfer catalyst (18-crown-6) (Scheme 2). Compounds **7a**−**c** (Table 1) were characterized by elemental analysis and NMR.

Cyano derivative **7a** reacted with 1,3-diphenylprop-2-en-1-one (**8a**) in the presence of diethylamine in ethanol to give 2-(diethylamino)-4,6-diphenylpyridine (**14a**) (64%) (Scheme 3). 2-(Disubstituted amino)pyridines **14b**−**k** (Table 2) with diverse substituents at the C(4) and C(6) positions of the pyridine ring were similarly synthesized in yields of 35−74%. In the series of 2-(disubstituted amino)pyridines **14** prepared, those containing a methyl

Scheme 3



substituent at the C(6) position, *i.e.*, **14i**−**k**, were obtained in lower yield in comparison to their C(6)-aryl-substituted analogs (**14a**−**h**). An extra aryl group evidently facilitates cyclization of intermediates **9**.

Reaction of cyano derivative **7a** with chalcone **8a** in ethanolic NaOH for 18 h at 20 °C gave after column chromatography 4,6-diphenylpyrid-2-one (**15a**, 47%) and 2-ethoxy-4,6-diphenylpyridine (**13a**, 15%) (Scheme 3). Compound **13a**, with a structure analogous to that of **3** (Scheme 1), is a probable intermediate that is hydrolyzed to pyrid-2-one **15a**. Alternatively, **15a** could be formed by direct nucleophilic attack of hydroxide anion rather than ethoxide anion as shown in Scheme 3. The analogous reaction of 4-phenylbut-3-en-2-one (**8h**) with 2-(benzotriazol-2-yl)acetonitrile (**7a**) gave only a low yield of 2-ethoxy-4-phenyl-6-methylpyridine (**13i**).

1,3-Disubstituted prop-2-en-1-ones **8a**−**g** reacted with 2-(benzotriazol-1-yl)acetamide (**7b**) to form the corresponding 4-phenyl-6-(substituted)pyrid-2-ones **15a**−**h** (53−92%) (Scheme 4, Table 3). A substituent in the α-position of the α,*β*-unsaturated ketones prevents formation of detectable amounts of pyrid-2-ones: attempts to use either 1,3-diphenyl-2-methylprop-2-en-1-one or 2-(benzylidene)cyclohexan-1-one failed. When 2-butyl- or 2-benzyl-2-(benzotriazol-1-yl)acetamides were employed in the reaction with chalcone **8a**, the corresponding 3-butyl- or 3-benzyl-4,6-diphenylpyrid-2-ones were detected in the reaction mixtures by GC/MS in less than 10% yields. The bulkier the substituent, the more difficult the formation of intermediate **16**.

The structures of compounds **15** were supported by ^1H and ^{13}C NMR spectra, GC/MS, and elemental analyses

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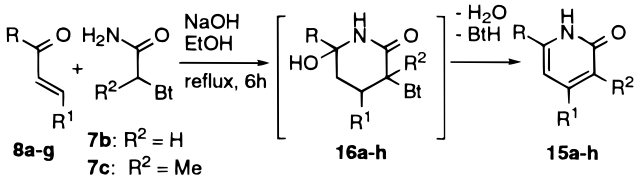
Table 2. Preparation of 2-(Disubstituted amino)pyridines 14

							elemental analysis found (required)		
compd **14**	R	R^1	R^2	yield, %	mp, °C (solvt)	molecular formula	C	H	N
a	Ph	Et	Et	64	112−113 (hexanes)	$C_{21}H_{22}N_2$	83.23 (83.40)	7.46 (7.33)	9.22 (9.26)
b	Ph	$-(CH_2)_4-$		74	161−162 (hexanes)	$C_{21}H_{20}N_2$	83.71 (83.96)	6.83 (6.71)	9.14 (9.33)
c	Ph	$-(CH_2)_5-$		68	130−131 (hexanes)	$C_{22}H_{22}N_2$	84.31 (84.04)	7.32 (7.05)	8.81 (8.91)
d	Ph	$-(CH_2)_2O(CH_2)_2-$		65	153−154 (hexanes/EtOAc)	$C_{21}H_{20}N_2O$	79.67 (79.72)	6.42 (6.37)	8.83 (8.85)
e	4-MeC_6H_4	Et	Et	66	99−100 (EtOH)	$C_{22}H_{24}N_2$	83.52 (83.50)	7.78 (7.64)	8.87 (8.85)
f	4-MeC_6H_4	$-(CH_2)_4-$		70	176−177 (EtOH)	$C_{22}H_{22}N_2$	83.76 (84.04)	7.08 (7.05)	8.86 (8.91)
g	4-MeC_6H_4	$-(CH_2)_5-$		64	134−135 (EtOH)	$C_{23}H_{24}N_2$	84.10 (84.11)	7.49 (7.36)	8.50 (8.53)
h	4-MeC_6H_4	$-(CH_2)_2O(CH_2)_2-$		56	153−154 (EtOAc)	$C_{22}H_{22}N_2O$	80.13 (79.97)	6.77 (6.71)	8.47 (8.48)
i	Me	Et	Et	43	oil	$C_{16}H_{20}N_2$			11.55[a] (11.66)
j	Me	$-(CH_2)_5-$		35	oil	$C_{17}H_{20}N_2$	80.78 (80.91)	8.18 (7.99)	10.97 (11.10)
k	Me	$-(CH_2)_2O(CH_2)_2-$		45	116−117 (hexanes)	$C_{16}H_{18}N_2O$	75.41 (75.56)	7.20 (7.13)	10.97 (11.01)

[a] MS: found 241.1701 [M + 1] calcd 241.1705 [M + 1].

Scheme 4



and also by the identity of the melting point of compound **15a** samples obtained according to the methods depicted in both Schemes 3 and 4.

A suggested mechanism for the formation of both 2-aminopyridines and pyrid-2-ones by the reaction of nitrile **7a** with chalcones **8** in the presence of bases (Scheme 3) involves intermediate Michael adducts **9** and **10**, which upon nucleophilic attack by either a *sec*-amine or an alcohol form the corresponding tetrahydropyridines **11** and **12**. Aromatization of the reaction intermediates occurs upon dehydration and loss of the benzotriazole molecule leading to the appropriate pyridines **14** and **13**. In the case of 2-ethoxypyridine **13**, the excess of a strong base promotes the loss of the alkoxy moiety and subsequent tautomerization of 2-hydroxypyridine into pyridone **15**.

Reaction of benzotriazole-containing amides **7b,c** with 1,3-disubstituted prop-2-en-1-ones **8** (Scheme 4) also involves analogous tandem reaction sequence. However, here the pyridone backbone is formed immediately after cyclization of Michael adduct into piperidin-2-one **16**, which undergoes dehydration and loss of benzotriazole to give the desired pyrid-2-ones **15a**−**h**.

In summary, CH-active benzotriazolyl derivatives of acetic acid **7a**−**c** react with α,β-unsaturated ketones to provide an efficient one-pot method for the regioselective preparation of both 2-(substituted amino)pyridines **14** and 3,4,6-substituted pyrid-2-ones **15**. This gives access to the *3-unsubstituted* pyridine derivatives, which were previously difficult to obtain. The formation of the heterocycle is the result of a [3 + 3] annulation reaction involving the addition of the CH-active compound to the double bond, followed by heterocyclization. The aromatization of the heterocycle thus formed is further assisted by the loss of the benzotriazole moiety, which enhances the synthetic applicability of our new methodology.

Experimental Section

General Methods. See refs[17,18] Substituted prop-2-en-1-ones **8b,c,g** were synthesized in accordance with literature procedure;[19] others were commercially available and were used as received. ^{1}H NMR spectra were recorded at 300 MHz in $CDCl_3$, except for compound **7c** (DMSO-d_6) and ^{13}C NMR spectra at 75 MHz in the same solvents, except for compounds **15d-f**, whose spectra were recorded in $CDCl_3$ containing 5% (v/v) of TFA. The ^{13}C NMR spectra of pyridones **15a**−**h** consist of a number of overlapped signals. The peak values are reported as observed.

2-(Benzotriazol-1-yl)acetonitrile (7a). A mixture of sodium benzotriazolate (8.46 g, 60 mmol), 2-chloroacetonitrile (4.53 g, 60 mmol), and 18-crown-6 (50 mg) in toluene (120 mL) was stirred at reflux for 18 h. On cooling, the mixture was washed with water, the organic layer was separated and dried over anhyd Na_2SO_4, and the solvent was removed *in vacuo* to give a crude product, which was recrystallized from benzene.

2-(Benzotriazol-1-yl)acetamide (7b). The product was prepared as described above from sodium benzotriazolate (2.54 g, 18 mmol), bromoacetamide (2.48 g, 18 mmol), and 18-crown-6 (25 mg) in refluxing toluene (60 mL). On cooling, the mixture was poured onto water (100 mL) and thoroughly stirred and the precipitate collected by filtration. The precipitate was washed with benzene and water and dried *in vacuo* to give the product as white needles. The analytical sample was obtained by recrystallization from ethyl acetate: ^{1}H NMR δ 5.43 (s, 2H), 7.40 (t, J = 7.5 Hz, 1H), 7.46 (br s, 1H), 7.55 (t, J = 7.6 Hz, 1H), 7.77 (d, J = 8.4 Hz, 1H), 7.86 (br s, 1H), 8.04 (d, J = 8.3 Hz, 1H); ^{13}C NMR δ 49.7, 110.9, 119.0, 123.8, 127.2, 133.8, 145.1, 167.5.

(±)-2-(Benzotriazol-1-yl)propionamide (7c). A mixture of sodium benzotriazolate (1.30 g, 9.2 mmol), (±)-2-bromopropionamide (**6**, X = Br, R = Me) (0.97 g, 6.4 mmol), and 18-crown-6 (50 mg) in toluene (30 mL) was stirred under reflux for 18 h. On cooling, water was added to the reaction mixture, and the precipitated crude product was collected by filtration, washed with water and toluene, and air dried. Recrystallization from methanol gave the benzotriazol-1-yl isomer of **7c** as a white solid (0.81 g, 67%): ^{1}H NMR δ 1.88 (d, J = 7.1 Hz,

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Table 3. Preparation of 3,4,6-Substituted Pyrid-2-ones 15

							elemental analysis found (required)		
pyridone **15**	R	R^1	R^2	yield, %	mp, °C (solvt)	molecular formula	C	H	N
a	C_6H_5	C_6H_5	H	92	216−217 (205−206)[a] (EtOAc)	$C_{17}H_{13}NO$			
b	4-MeC_6H_4	C_6H_5	H	85	238−239 (MeOH)	$C_{18}H_{15}NO$	82.44 (82.73)	5.67 (5.79)	5.31 (5.36)
c	4-$MeOC_6H_4$	4-MeC_6H_4	H	54	258−260 (EtOAc)	$C_{19}H_{17}NO_2$	78.04 (78.33)	5.96 (5.88)	4.61 (4.81)
d	C_6H_5	4-$O_2NC_6H_4$	H	57	281−282 (acetone)	$C_{17}H_{12}N_2O_3$	(69.86)	(4.14)	9.56[b] (9.58)
e	C_6H_5	4-ClC_6H_4	H	53	237−238 (acetone)	$C_{17}H_{12}ClNO$	72.35 (72.47)	4.23 (4.29)	4.96 (4.97)
f	4-ClC_6H_4	4-ClC_6H_4	H	75	308−309 (acetone)	$C_{17}H_{11}Cl_2NO$	64.66 (64.58)	3.50 (3.51)	4.38 (4.43)
g	1-naphthyl	3-$O_2NC_6H_4$	H	31	218−220 (EtOAc)	$C_{21}H_{14}N_2O_3$	(73.68)	(4.12)	[c] (7.86)
h	C_6H_5	C_6H_5	Me	53	248−249 ($CHCl_3$)	$C_{18}H_{15}NO$	82.48 (82.73)	5.94 (5.79)	5.35 (8.18)

[a] Lit.[16] mp. [b] MS: found 292.0838 [M^+], calcd 292.0848 [M^+]. [c] MS: found 343.1076 [M + 1], calcd 343.1083 [M + 1].

3H), 5.67 (q, J =7.1 Hz, 1H), 7.36−7.48 (m, 2H), 7.53 (t, J = 7.1 Hz, 1H), 7.75−7.85 (m, 2H), 8.04 (d, J = 8.3 Hz, 1H); ^{13}C NMR δ 16.8, 57.4, 111.2, 119.1, 123.9, 127.1, 132.7, 145.5, 170.3.

General Procedure for the Preparation of 2-(Disubstituted amino)pyridines 14a−k. To a stirred solution of 1-(cyanomethyl)benzotriazole (**7a**) (0.395 g, 2.5 mmol) and the corresponding 1-substituted 3-phenylprop-2-en-1-one **8** (2.5 mmol) in ethanol (8 mL) was added a corresponding *sec*-amine (2 mL), and the resulting solution was stirred under reflux for 48 h. The solvent was removed under reduced pressure, and the residue was dissolved in CH_2Cl_2 (10 mL), washed with 10% NaOH (2 × 5 mL) and brine, and dried over anhyd Na_2SO_4, and the solvent was removed *in vacuo*. Column chromatography of the crude product (silica gel, eluent hexane: ethyl acetate 5:1) gave the corresponding pyridine **14a**−**k**. The properties of the prepared pyridines are shown in Table 2.

2-(Diethylamino)-4,6-diphenylpyridine (14a): ^{1}H NMR δ 1.26 (t, J = 7.1 Hz, 6H), 3.65 (q, J = 7.1 Hz, 4H), 6.58 (s, 1H), 7.20 (s, 1H), 7.34−7.49 (m, 6H), 7.64 (d, J = 6.7 Hz, 2H), 8.10 (d, J = 7.0 Hz, 2H); ^{13}C NMR δ 13.2, 42.7, 102.2, 106.7, 126.8, 127.1, 128.3, 128.4, 128.8, 140.4, 140.6, 150.6, 155.7, 157.8.

2-(Pyrrolidin-1-yl)-4,6-diphenylpyridine (14b): ^{1}H NMR δ 1.99−2.03 (m, 4H), 3.57−3.62 (m, 4H), 6.47 (d, J = 1.1 Hz, 1H), 7.23 (d, J = 1.1 Hz, 1H), 7.33−7.48 (m, 6H), 7.66 (d, J = 6.6 Hz, 2H), 8.10 (d, J = 7.3 Hz, 2H); ^{13}C NMR δ 25.6, 47.8, 103.0, 106.9, 126.9, 127.1, 128.3, 128.4, 128.8, 140.3, 150.3, 155.9, 157.7.

2-(Piperidin-1-yl)-4,6-diphenylpyridine (14c): ^{1}H NMR δ 1.62−1.80 (m, 6H), 3.67−3.69 (m, 4H), 6.77 (d, J = 1.0 Hz, 1H), 7.26 (d, J = 1.0 Hz, 1H), 7.34−7.48 (m, 6H), 7.64 (d, J = 6.6 Hz, 2H), 8.07 (d, J = 7.0 Hz, 2H); ^{13}C NMR δ 24.9, 25.6, 46.4, 103.7, 108.1, 126.9, 127.1, 128.4, 128.5, 128.8, 140.2, 140.3, 150.9, 155.7, 159.9.

2-(Morpholin-1-yl)-4,6-diphenylpyridine (14d): ^{1}H NMR δ 3.63−3.67 (m, 4H), 3.84−3.87 (m, 4H), 6.74 (s, 1H), 7.35 (s, 1H), 7.37−7.48 (m, 6H), 7.63 (d, J = 6.6 Hz, 2H), 8.06 (d, J = 7.0 Hz, 2H); ^{13}C NMR δ 45.7, 66.8, 103.5, 109.4, 126.8, 127.1, 128.4, 128.6, 128.7, 128.8, 139.8, 139.9, 151.1, 155.8, 159.7.

2-(Diethylamino)-4-phenyl-6-(4-tolyl)pyridine (14e): ^{1}H NMR δ 1.58 (t, J = 7.1 Hz, 6H), 2.71 (s, 3H), 4.00 (q, J = 7.1 Hz, 4H), 6.88 (s, 1H), 7.50 (s, 1H), 7.56 (d, J = 8.3 Hz, 2H), 7.71−7.81 (m, 3H), 7.96 (d, J = 7.1 Hz, 2H), 8.26 (d, J = 8.0 Hz, 2H); ^{13}C NMR δ 13.2, 21.2, 42.7, 101.9, 106.3, 126.7, 127.1, 128.2, 128.7, 129.1, 137.7, 138.2, 140.7, 150.6, 155.7, 157.7.

2-(Pyrrolidin-1-yl)-4-phenyl-6-(4-tolyl)pyridine (14f): ^{1}H NMR δ 1.99−2.04 (m, 4H), 2.39 (s, 3H), 3.57−3.62 (m, 4H), 6.46 (s, 1H), 7.20 (s, 1H), 7.24 (d, J = 8.0 Hz, 2H), 7.36−7.48 (m, 3H), 7.66 (d, J = 6.8 Hz, 2H), 8.00 (d, J = 8.0 Hz, 2H); ^{13}C NMR δ 21.3, 25.6, 46.8, 102.7, 106.6, 126.8, 127.1, 128.3, 128.7, 129.1, 137.6, 138.2, 140.4, 150.3, 155.9, 157.7.

2-(Piperidin-1-yl)-4-phenyl-6-(4-tolyl)pyridine (14g): ^{1}H NMR δ 1.67 (m, 6H), 2.38 (s, 3H), 3.67−3.68 (m, 4H), 6.75 (s, 1H), 7.20−7.25 (m, 3H), 7.38−7.47 (m, 3H), 7.63 (d, J = 6.7 Hz, 2H), 7.97 (d, J = 8.2 Hz, 2H); ^{13}C NMR δ 21.2, 24.9, 25.6, 46.4, 103.4, 107.8, 126.8, 127.1, 128.3, 128.8, 129.1, 137.5, 138.3, 140.4, 150.8, 155.7, 159.9.

2-(Morpholin-1-yl)-4-phenyl-6-(4-tolyl)pyridine (14h): ^{1}H NMR δ 2.42 (s, 3H), 3.69−3.70 (m, 4H), 3.90−3.91 (m, 4H), 6.75 (s, 1H), 7.29 (d, J = 6.8 Hz, 2H), 7.36 (s, 1H), 7.47−7.50 (m, 3H), 7.66 (d, J = 6.9 Hz, 2H), 7.99 (d, J = 7.0 Hz, 2H); ^{13}C NMR δ 21.3, 45.8, 66.9, 103.2, 109.1, 126.8,127.1, 128.6, 128.8, 129.2, 137.0, 138.6, 140.0, 151.1, 155.8, 159.7.

2-(Diethylamino)-4-phenyl-6-methylpyridine (14i): ^{1}H NMR δ 1.19 (t, J = 7.1 Hz, 6H), 2.43 (s, 3H), 3.56 (q, J = 7.1 Hz, 4H), 6.43 (s, 1H), 6.58 (s, 1H), 7.32−7.43 (m, 3H), 7.56−7.58 (m, 2H); ^{13}C NMR δ 13.0, 24.8, 42.3, 100.3, 109.1, 127.0, 128.1, 128.6, 140.5, 150.0, 157.2, 157.8.

2-(Piperidin-1-yl)-4-phenyl-6-methylpyridine (14j): ^{1}H NMR δ 1.64−1.67 (m, 6H), 2.45 (s, 3H), 3.56−3.57 (m, 4H), 6.62 (s, 1H), 6.66 (s, 1H), 7.34−7.45 (m, 3H), 7.55−7.59 (m, 2H); ^{13}C NMR δ 24.7, 24.8, 25.6, 46.5, 102.0, 110.7, 127.0, 128.2, 128.7, 140.2, 150.3, 157.1, 160.1.

2-(Morpholin-1-yl)-4-phenyl-6-methylpyridine (14k): ^{1}H NMR δ 2.47 (s, 3H), 3.56 (t, J = 4.9 Hz, 4H), 3.85 (t, J = 4.8 Hz, 4H), 6.61 (s, 1H), 6.77 (s, 1H), 7.35−7.49 (m, 3H), 7.58 (d, J = 9.0 Hz, 2H); ^{13}C NMR δ 24.7, 46.0, 66.9, 101.9, 112.2, 127.1, 128.5, 128.8, 139.9, 150.7, 157.3, 160.0.

Reaction of 2-(Benzotriazol-1-yl)acetonitrile (7a) with 1,3-Diphenylprop-2-en-1-one (8a) in the Presence of NaOH. Compounds **7a** (0.26 g, 1.8 mmol) and **8a** (0.37 g, 1.8 mmol) were added at rt to a stirred solution of NaOH (0.36 g, 9.0 mmol) in ethanol (5 mL). After 18 h, the reaction mixture was diluted with water (20 mL), and the formed precipitate A was filtered, washed with water, and air dried. To the filtrate was added a solution of HCl (4 N, 20 mL), the resulting mixture was stirred for 2 h, and the precipitate B was filtered, washed with water, and air dried. Both crude products were subjected to column chromatography: product A on silica gel using hexanes:CH_2Cl_2 1:1 as eluting system afforded 0.073 g (15%) of the 2-ethoxy-4,6-diphenylpyridine (**13a**); product B on silica gel using MeOH:$CHCl_3$ 1:20 as eluting system afforded 0.210 g (47%) of the 4,6-diphenylpyrid-2-one (**15a**), mp 216−218 °C (ethyl acetate). Spectral characteristics and mp of **15a** are consistent with those determined for another sample of this product obtained by the procedure described below.

2-Ethoxy-4,6-diphenylpyridine (13a): prisms; mp 56−57 °C; ^{1}H NMR δ 1.45 (t, J = 7.1 Hz, 3H), 4.53 (q, J = 7.1 Hz, 2H), 6.86 (d, J = 1.2 Hz, 1H), 7.37−7.48 (m, 6H), 7.53 (d, J = 1.2 Hz, 1H), 7.63 (d, J = 6.6 Hz, 2H), 8.07 (d, J = 6.9 Hz, 2H); ^{13}C NMR δ 14.8, 61.7, 107.1, 111.6, 126.8, 127.0, 128.6, 128.8, 128.9, 138.8, 139.3, 151.9, 155.1, 164.2. Anal. Calcd for

$C_{19}H_{17}NO$: C, 82.88; H, 6.22; N, 5.09. Found: C, 82.95; H, 6.41; N, 4.96.

General Procedure for the Preparation of 3,4,6-Substituted Pyrid-2-ones 15a−h. A mixture of the corresponding benzotriazolyl derivative of acet- or propionamide **7b,c** (0.46 mmol), 1,3-diarylprop-3-en-2-one **8a−g** (0.46 mmol), and NaOH (43 mg, 1.08 mmol) in ethanol (10 mL) was stirred at reflux for 6 h. On cooling, water (15 mL) and HCl (4 N, 15 mL) were added to the mixture. The precipitated crude product was filtered, washed with water, and air dried. Trituration with an appropriate solvent (see Table 3) gave the corresponding pyrid-2-one **15a−h** as a crystalline solid. The properties of the obtained pyrid-2-ones are given in Table 3.

4,6-Diphenylpyrid-2-one (15a): ^{1}H NMR δ 6.75−6.77 (m, 2H), 7.43−7.55 (m, 6H), 7.63−7.66 (m, 2H), 7.80−7.83 (m, 2H), 12.67 (br s, 1H); ^{13}C NMR δ 104.8, 115.3, 126.9, 128.9, 129.1, 129.4, 130.0, 133.8, 138.2, 146.9, 153.7, 165.6.

4-Phenyl-6-(4-methylphenyl)pyrid-2-one (15b): ^{1}H NMR δ 2.41 (s, 3H), 6.72 (d, J = 1.6 Hz, 1H), 6.74 (d, J = 1.6 Hz, 1H), 7.31−7.33 (m, 2H), 7.43−7.50 (m, 3H), 7.62−7.71 (m, 4H), 12.45 (br s, 1H); ^{13}C NMR δ 21.3, 104.3, 114.9, 126.7, 126.9, 128.9, 129.4, 129.9, 130.9, 138.3, 140.3, 146.9, 153.7, 165.5.

4-(4-Methylphenyl)-6-(4-methoxyphenyl)pyrid-2-one (15c): ^{1}H NMR δ 2.42 (s, 3H), 3.88 (s, 3H), 6.67 (s, 1H), 6.69 (s, 1H), 7.04 (d, J = 9.0 Hz, 2H), 7.28 (d, J = 9.9 Hz, 2H), 7.54 (d, J = 8.1 Hz, 2H), 7.70 (d, J = 8.7 Hz, 2H); ^{13}C NMR δ 21.4, 55.7, 108.9, 111.6, 115.4, 123.6, 127.3, 128.8, 130.4, 132.6, 142.5, 148.5, 159.6, 162.7.

4-(4-Nitrophenyl)-6-phenylpyrid-2-one (15d): ^{1}H NMR δ 6.80 (s, 1H), 7.12 (s, 1H), 7.46−7.56 (m, 3H), 7.92−7.94 (m, 2H), 8.12 (d, J = 8.5 Hz, 2H), 8.32 (d, J = 8.5 Hz), 12.0 (br s, 1H); ^{13}C NMR δ 111.4, 124.8, 127.1, 128.6, 130.0, 130.9, 132.3, 142.1, 149.2, 149.4, 156.6, 163.7.

4-(4-Chlorophenyl)-6-phenylpyrid-2-one (15e): ^{1}H NMR δ 6.68 (s, 1H), 7.02 (s, 1H), 7.46−7.53 (m, 3H), 7.56 (d, J = 8.3 Hz, 2H), 7.86 (d, J = 8.5 Hz, 2H), 7.90−7.94 (m, 2H), 11.7 (br s, 1H); ^{13}C NMR δ 111.0, 111.6, 127.2, 128.6, 129.9, 130.0, 131.2, 132.0, 134.0, 138.1, 148.9, 158.0, 163.3.

4,6-Bis(4-chlorophenyl)pyrid-2-one (15f): ^{1}H NMR δ 6.73 (s, 1H), 7.15 (s, 1H), 7.56 (d, J = 8.3 Hz, 4H), 7.87 (d, J = 8.5 Hz, 2H), 7.97 (d, J = 8.3 Hz), 11.6 (br s, 1H); ^{13}C NMR δ 111.3, 111.5, 128.5, 128.6, 129.6, 130.0, 130.2, 133.9, 138.2, 138.7, 147.6, 158.0, 163.5.

4-(3-Nitrophenyl)-6-(naphth-1-yl)pyrid-2-one (15g): ^{1}H NMR δ 6.66 (s, 1H), 6.74 (s, 1H), 7.48−7.72 (m, 5H), 7.84−8.04 (m, 4H), 8.30 (d, J = 8.1 Hz, 1H), 8.46 (s, 1H), 12.50 (br s, 1H); ^{13}C NMR δ 107.0, 116.4, 121.9, 124.1, 124.5, 125.2, 126.6, 127.4, 127.5, 128.8, 130.1, 130.7, 131.6, 132.7, 133.9, 139.7, 146.9, 148.8, 150.9, 164.3.

3-Methyl-4,6-diphenylpyrid-2-one (15h): ^{1}H NMR δ 2.13 (s, 3H), 6.50 (s, 1H), 7.25−7.49 (m, 8H), 7.80−7.82 (m, 2H), 12.30 (br s, 1H); ^{13}C NMR δ 13.5, 107.2, 124.4, 126.5, 128.0, 128.2, 128.4, 129.0, 129.6, 133.6, 139.9, 142.4, 151.4, 165.4.

Supporting Information Available: ^{1}H and ^{13}H NMR spectra for compounds **14i** and **15d,g** (9 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS: see any current masthead page for ordering information.

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