Hydrazine-Mediated One-Pot Amination-Oxidation Reaction: Facile Synthesis of 4-Amino-β-carbolines and 4-Aminoisoquinolines

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The conversion of the 4-oxo-2-benzoyl-1,2,3,4-tetrahydro-β-carbolines **1a** and **1b**, respectively, into their corresponding 4-amino-β-carbolines **2a** and **2b** was effected in 70% yield in refluxing hydrazine. In contrast, phenylhydrazine, when heated with the 4-oxo derivative **1b**, gave the pyridodiindole **18a**. This compound derives its origin from an initial Fischer indole cyclization, followed by loss of the 2-benzoyl group and aromatization to the β-carboline. During investigation of the scope and mechanism of this new amination–oxidation reaction, it was found that an acidic hydrogen atom (position 2, NH) γ to the carbonyl group (C-4) was necessary to drive the reaction to completion. Although phenylhydrazones such as **20b** and **20c**, which carry electron-withdrawing groups, led to the formation of **2b** at the expense of the Fischer indole products **18b** and **18c**, respectively, the yields in this sequence were only moderate. Hydrazine, consequently, appears to be the reagent of choice to effect this amination–oxidation reaction since Fischer indole cyclization cannot compete in this process.

During studies directed toward the synthesis of the naturally occurring β-carboline alkaloid crenatine, it was found that 1-ethyl-2-benzoyl-4-oxo-1,2,3,4-tetrahydro-β-carboline (**1a**) could be converted into 1-ethyl-4-amino-β-carboline (**2a**) upon heating **1a** in excess hydrazine.[1] The yield and ease of this one-pot amination–oxidation reaction prompted an investigation into the scope and limitations of this process.

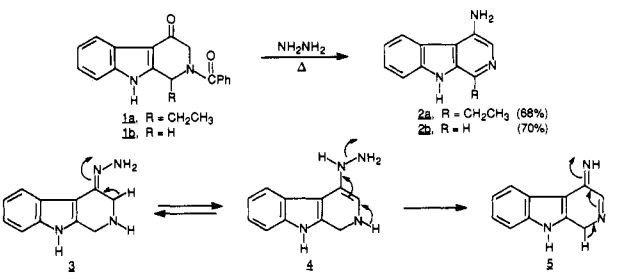
Results and Discussion

2-Benzoyl-4-oxo-1,2,3,4-tetrahydro-β-carboline (**1b**) was prepared from tryptamine by a method developed in our laboratories.[1] When **1b** was heated in excess hydrazine at reflux for 12 h, the amination–oxidation reaction took place to provide 4-amino-β-carboline (**2b**) in 70% yield.[2] The proposed mechanism for this conversion is shown for **1b** at the bottom of Scheme I. The removal of the benzoyl group of **1b** by hydrazine, accompanied by simultaneous formation of the hydrazone **3**, followed by the steps indicated (**3**–**5**), would result in the generation of ammonia, accompanied by the desired 4-amino-β-carboline (**2b**). Hydrazine, therefore, serves as the oxidizing agent in this process.

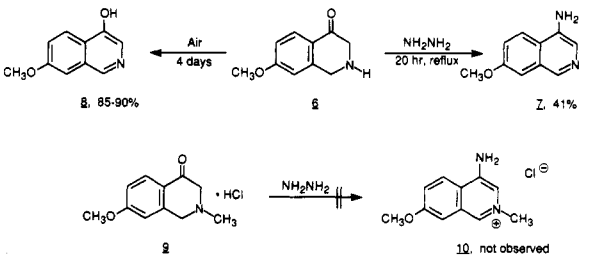
Our attention turned toward extending the synthetic utility of this hydrazine reaction to the analogous isoquinoline series. 4-Oxo-7-methoxy-1,2,3,4-tetrahydroisoquinoline (**6**) was prepared by the method of Grethe.[3] As illustrated in Scheme II, treatment of **6** with excess hydrazine at reflux for 20 h gave the desired amination–oxidation product, 4-amino-7-methoxyisoquinoline (**7**), in 41% yield. The low yield of this process is due to the inherent lability of **6** toward oxidation. When **6** was simply allowed to stand as a solid in the presence of air for several days, a nearly quantitative conversion into 4-hydroxy-7-methoxyisoquinoline (**8**) occurred. Nonetheless, the hydrazine-mediated conversion of **6** into **7** may provide an alternate pathway to isoquinoline analogues of chloroquine.[4]

Examination of the proposed mechanism for this sequence, as outlined in Scheme I, clearly indicates that the presence of an acidic hydrogen atom γ (2-position, NH) to the carbonyl moiety is required for the amination–oxidation reaction. Cleavage of the 2-benzoyl group of the β-carboline derivative by hydrazine provides the necessary acidic hydrogen atom as an NH group to promote oxidation of ring C of the β-carboline nucleus. Similarly, the presence of the NH function in the isoquinoline derivative

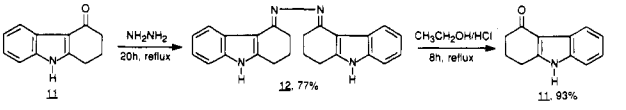
Scheme I



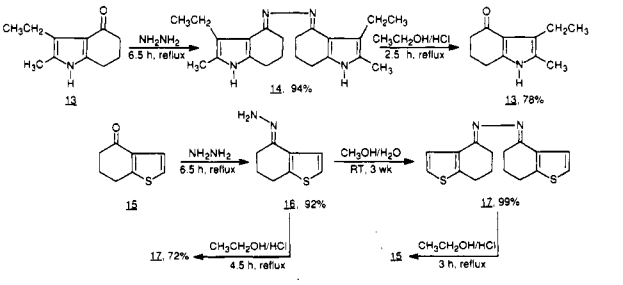
Scheme II



Scheme III



Scheme IV



(1) Cain, M.; Mantei, R.; Cook, J. M. *J. Org. Chem.* **1982**, *47*, 4933–4936.

(2) Fukada, N.; Trudell, M. L.; Johnson, B.; Cook, J. M. *Tetrahedron Lett.* **1985**, *26* 2139–2142.

(3) Grethe, G.; Lee, H. L.; Uskokovic, M.; Brossi, A. *J. Org. Chem.* **1968**, *33*, 491–494.

(4) (a) Schmidt, L. H. *Annu. Rev. Microbiol.* **1969**, *23*, 427. (b) Peters, W. *Trop. Dis. Bull.* **1967**, *64*, 1145. (c) Thompson, P. E. *Annu. Rev. Pharmacol.*, **1967**, *7*, 77. (d) Powell, R. D.; Tigertt, W. D. *Annu. Rev. Med.* **1968**, *19*, 81 and references contained therein.

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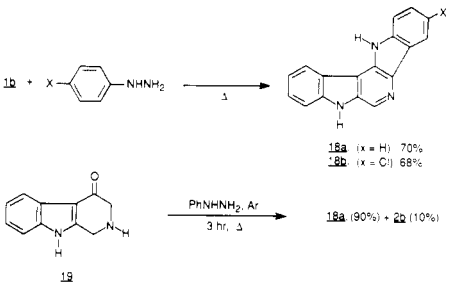
is necessary for successful completion of the amination–oxidation process. In agreement with this, Mann et al.[5] reported that 2-methyl-4-oxo-1,2,3,4-tetrahydroisoquinoline hydrochloride (**9**) gave none of the desired isoquinolinium cation **10** when heated in excess hydrazine, even after extended reaction times. To investigate further the effect of the acidic hydrogen atom γ to the carbonyl functionality on the progress of the reaction, 4-oxo-1,2,3,4-tetrahydrocarbazole (**11**) was heated in excess hydrazine (Scheme III). After extended reaction times, only the azine derivative **12** was isolated from the reaction mixture. In other examples, 3-ethyl-2-methyl-4-oxo-4,5,6,7-tetrahydroindole (**13**) and 4-oxo-4,5,6,7-tetrahydrothianaphthene (**15**) were each heated in an excess of refluxing hydrazine; the results are illustrated in Scheme IV. However, even after extended reaction times, neither the desired 4-aminoindole derivative nor the 4-aminothianaphthene derivative, respectively, was formed in this reaction. These results further demonstrate the necessary presence of an acidic hydrogen γ to the carbonyl group at position 4 in order to drive the amination–oxidation to completion.

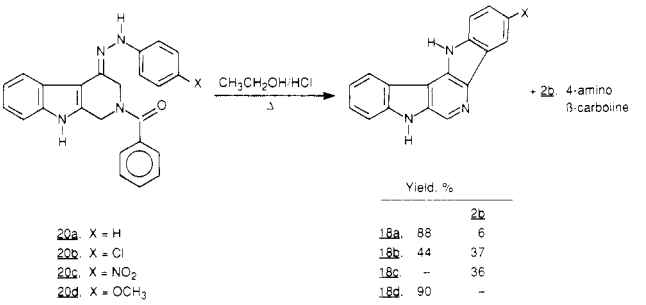
It had been shown that **9** could not be converted into **10** in refluxing hydrazine. However, it had been reported[5] that the phenylhydrazone of **9**, when heated in ethanolic hydrogen chloride, did provide the 2-methyl-4-aminoisoquinolinium salt **10**. The difference in reactivity between the two systems is due, presumably, to the stability of aniline generated by the dismutation of the phenylhydrazone vs. that of ammonia that would result from the reaction of **9** with hydrazine. Since Mann et al.[5] achieved some success with refluxing ethanolic hydrogen chloride, the three azines **12**, **14**, and **17** were heated, individually, in refluxing ethanolic hydrogen chloride. Again, only the starting ketones were isolated. This resulted from hydrolysis of the azine derivatives upon workup. In a similar attempt, the hydrazone **16** was heated in refluxing ethanolic hydrogen chloride for several hours; however, only the crystalline azine **17** (72% yield) was isolated from the reaction mixture.

Although the 4-amino-β-carboline derivatives could be prepared in reasonably good yield via the reaction with hydrazine, the work of Mann using phenylhydrazine (CH_3CH_2OH, HCl, **9** to **10**) seemed a viable alternative.[5] 2-Benzoyl-4-oxo-1,2,3,4-tetrahydro-β-carboline (**1b**) was heated for 6 h in excess phenylhydrazine under conditions analogous to those employed for the hydrazine reaction. The compound produced cleanly from this sequence in 70% yield was the undesired, but interesting, 7,12-dihydropyrido[3,2-*b*:5,4-*b*′]diindole (**18a**). This base can be viewed as the product of a Fischer indole cyclization,[6] followed by cleavage of the benzoyl group and aromatization of ring C of the β-carboline. The reaction was then performed with (4-chlorophenyl)hydrazine. It was felt that the chloro substituent would deactivate the phenyl ring enough to inhibit the Fischer indole cyclization and therefore favor dismutation to 4-chloroaniline and the amination–oxidation product **2b**. However, when **1b** was heated in excess (4-chlorophenyl)hydrazine, the corresponding diindole **18b** was obtained as the major product as illustrated in Scheme V. Only a small amount (5–10%) of the 4-amino-β-carboline (**2b**) was observed in the reaction mixture. When phenylhydrazines were employed under thermal conditions, the Fischer indole cyclization was favored over cleavage of the benzoyl group, followed by the dismutation to aniline and **2b**. It seemed that the necessary removal of the benzoyl group by phenylhydrazine retarded the formation of the 4-amino-β-carboline. In order to determine to what extent this was the case, 4-oxo-1,2,3,4-tetrahydro-β-carboline (**19**) was heated in an excess of phenylhydrazine. But, even in the absence of the benzoyl group, the Fischer indolization was favored over the amination–oxidation reaction with the pyridodiindole **18a** comprising 90% of the product mixture, while the remaining 10% was made up of 4-amino-β-carboline **2b** (Scheme V). These results confirmed the fact that under thermal conditions the reactions of 4-oxo-1,2,3,4-tetrahydro-β-carboline derivatives with substituted phenylhydrazines favor Fischer indole cyclization over the amination–oxidation reaction.

Scheme V



Scheme VI



	Yield, %	
	18	2b
20a, X = H	88	6
20b, X = Cl	44	37
20c, X = NO_2	–	36
20d, X = OCH_3	90	–

In a final attempt to minimize the formation of the pyridodiindoles **18a–d**, the phenylhydrazones **20a–d** were prepared in situ and subjected to the reaction conditions of Mann et al.[5] (CH_3CH_2OH, HCl). The results are summarized in Scheme VI. Although this modification was successful in producing the 4-amino-β-carboline, once again the major product from this process was the result of a Fischer indole cyclization. Deactivation of the phenyl ring toward the Fischer indole cyclization with electron-withdrawing substituents did increase the amount of the amination–oxidation product relative to that of the Fischer product [X = Cl: **18b** (44%), **2b** (37%). X = NO_2: **18c** (0%), **2b** (36%)]; however, the overall yields are decreased (see Scheme VI). As anticipated, activation of the phenyl ring by an electron-releasing substituent (**20d**, X = OCH_3) gave the Fischer indolization product **18d** (90%) exclusively.[6] In all cases examined, phenylhydrazines were less efficient than hydrazine in promoting the amination–oxidation reaction.

In summary, the hydrazine-mediated amination–oxidation of 4-oxo-1,2,3,4-tetrahydro-β-carbolines and 4-oxo-1,2,3,4-tetrahydroisoquinolines proceeds smoothly in refluxing hydrazine to provide the corresponding 4-amino-β-carbolines and 4-aminoisoquinolines cleanly with minimal workup. For the reaction to proceed, in a practical sense, the substrate requires the presence of an acidic hydrogen (NH) γ to the carbonyl group in the ring undergoing reaction.[7] In the 4-oxotetrahydro-β-carboline

(5) Mann, F. G.; Hinton, I. G. *J. Chem. Soc.* **1959**, 599–610.
(6) For reviews see: (a) Robinson, B. *Chem. Rev.* **1963**, *63*, 373. (b) Robinson, B. *Chem. Rev.* 1969, *69*, 227.

series and presumably in the 4-oxotetrahydroisoquinoline series, hydrazine is far superior to phenylhydrazine, since the Fischer indole cyclization cannot compete as a side reaction in the former case.

Experimental Section

Microanalyses were performed on an F & M Scientific Corp. Model 185 carbon, hydrogen, and nitrogen analyzer. Melting points were taken on a Thomas-Hoover melting point apparatus; they are uncorrected. NMR spectra were recorded on a Bruker WM 250-MHz spectrometer. IR spectra were taken on a Beckman Aculab-1 instrument. Chemical ionization (CI, CH_4) mass spectra were obtained by using a Hewlett-Packard 5855 gas chromatograph mass spectrometer. The analytical TLC plates used were E. M. Scientific UV-active silica gel on plastic sheets. All chemicals were purchased from Aldrich Chemical Co.

Hydrazine-Mediated Amination–Oxidation Reactions (General Procedure). The 4-oxotetrahydro-β-carboline derivatives **1a,b** or the 4-oxo-7-methoxytetrahydroisoquinoline **6** (3 mmol) was added to anhydrous hydrazine (25 mL). The mixture was then heated in refluxing hydrazine for 12 h under an argon atmosphere. The mixture was then cooled to room temperature, and the excess hydrazine was removed under reduced pressure. The oily residue that remained was then dissolved in $CHCl_3$ (50 mL) and washed with water (3 × 50 mL). The organic layer was dried (Na_2SO_4), and the solvent was removed under reduced pressure to give an oil. The oil could then be crystallized from EtOAc or converted into an appropriate salt.

4-Amino-β-carboline (2b): 70%; mp 222–224 °C; MS (CI, CH_4) *m/e* 184 (M + 1); ^{1}H NMR (DMSO-d_6) δ 11.39 (s, 1 H), 8.36 (d, 1 H, *J* = 8 Hz), 8.19 (s, 1 H), 7.82 (s, 1 H), 7.54 (d, 1 H, *J* = 7.8 Hz), 7.47 (t, 1 H, *J* = 6.9 Hz), 7.22 (t, 1 H, *J* = 7.1 Hz), 5.78 (s, 2 H, br); exact mass calcd. for $C_{11}H_9N_3$ 183.0796, found: 183.0800. The dihydrochloride salt of **2b** was prepared; mp 312–315 °C. Anal. Calcd for $C_{11}H_9N_3 \cdot 2HCl$: C, 51.58; H, 4.33; N, 16.51. Found: C, 51.51; H, 4.46; N, 16.81.

4-Amino-7-methoxyisoquinoline (7): 41%; mp 137–140 °C dec; MS (CI, CH_4) *m/e* 175 (M + 1); exact mass calcd for $C_{10}H_{10}N_2O$ 174.0793, found 174.0801. The hydrochloride salt of **7** was prepared; mp 267–270 °C dec. Anal. Calcd for $C_{10}H_{10}N_2 \cdot HCl \cdot H_2O$: C, 52.52; H, 5.73; N, 12.25. Found: C, 52.38; H, 5.55; N, 12.16.

Bis[1,2,3,4-tetrahydrocarbazol-4-ylidene]hydrazine (12). A mixture of 4-oxo-1,2,3,4-tetrahydrocarbazole (**11**) (100 mg, 0.54 mmol) and anhydrous hydrazine (5 mL) was heated at reflux for 20 h. The mixture was then cooled to room temperature, and the excess hydrazine was removed in vacuo. The resulting oil was stirred with $CHCl_3$ (10 mL), and the precipitate that resulted was recrystallized from benzene/CH_3OH(aq) to give a yellow powder **12**: 80 mg (77%); mp >350 °C; IR (KBr) 3400, 1620, 1500, 1370 cm^{-1}; ^{1}H NMR (DMSO-d_6) δ 11.39 (s, 2 H), 8.19 (d, *J* = 3.0 Hz, 2 H), 7.34 (d, *J* = 3.5 Hz, 2 H), 7.10 (t, *J* = 3.0 Hz, 4 H), 3.08 (t, *J* = 6.0 Hz, 4 H), 2.90 (t, *J* = 6.0 Hz, 4 H), 2.05 (t, *J* = 5.5 Hz, 4 H); exact mass calcd for $C_{24}H_{22}N_4$ 366.1844, found 366.1842. Anal. Calcd for $C_{24}H_{22}N_4 \cdot H_2O$: C, 74.96; H, 6.29; N, 14.57. Found: C, 75.00; H, 6.01; N, 14.46.

Bis[3-ethyl-2-methyl-4,5,6,7-tetrahydroindol-4-ylidene]hydrazine (14). A mixture of 3-ethyl-2-methyl-4,5,6,7-tetrahydroindol-4-one (**13**) (250 mg, 1.41 mmol) and anhydrous hydrazine (25 mL) was heated at reflux for 6.5 h. The mixture was then cooled to room temperature and poured into water (100 mL). The resulting solution was extracted with $CHCl_3$ (3 × 30 mL), and the combined organic fractions were dried (Na_2CO_3). The solvent was removed in vacuo to give an orange solid **14**: 240 mg (94%); mp 303–305 °C dec; IR (KBr) 3360, 1610 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 4.70 (br, 2 H), 2.95–1.72 (m, 16 H), 2.08 (s, 6 H), 1.02 (t, 6 H, *J* = 7.0 Hz); MS (CI, CH_4), *m/e* 351 (M + 1). Anal. Calcd for $C_{22}H_{30}N_4 \cdot {}^1/_4H_2O$: C, 74.43; H, 8.66; N, 15.78. Found: C, 74.74; H, 8.61; N, 15.84.

Bis[4,5,6,7-tetrahydrothianaphthen-4-ylidene]hydrazine (17). A solution of the hydrazone **16** (50 mg) in methanol/water (3 mL, 1:1) was allowed to stand at room temperature for 1 week. This process gave yellow crystals of **17** in quantitative yield: mp 174–176 °C; IR (KBr) 1600 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.52 (d, 2 H, *J* = 5.4 Hz), 7.06 (d, 2 H, *J* = 5.4 Hz), 2.88 (t, 4 H, *J* = 6.0 Hz), 2.78 (t, 4 H, *J* = 6.0 Hz), 2.00 (q, 4 H, *J* = 6.1 Hz); MS (15 eV), *m/e* (relative intensity) 300 (100), 150 (12.4), 149 (13.5). Anal. Calcd for $C_{16}H_{16}N_2S_2$: C, 63.96; H, 5.37; N, 9.32. Found: C, 64.07; H, 5.41; N, 9.39.

The hydrazone **17** was also prepared by heating **16** (100 mg, 0.60 mmol) in a saturated solution of ethanolic hydrogen chloride at reflux for 4.5 h. The reaction mixture was then cooled to room temperature, and the hydrazine dihydrochloride that precipitated from the medium was filtered off. The filtrate was then concentrated to a yellow oil that was crystallized from H_2O to give **17**, 65 mg (72%).

Reaction of 1b with Substituted Phenylhydrazines under Thermal Conditions. Formation of 18a and 18b. A solution of **1b** (0.50g, 1.7 mmol) and the phenylhydrazine (38.0 mmol) was stirred at 200 °C for 12 h. The reaction mixture was then cooled to room temperature, and the excess phenylhydrazine was removed via vacuum distillation. The resulting oil was then precipitated with $CHCl_3$ (5 mL). The solid that formed was recrystallized from CH_3OH/CH_3CN (1:2) to provide 7,12-dihydropyrido[3,2-*b*:5,4-*b'*]diindole (**18a**): 70%; mp >350 °C; IR (KBr) 3380, 3250, 1610, 1575, 1410 cm^{-1}; MS (CI, CH_4), *m/e* 258 (M + 1); ^{1}H NMR (DMSO-d_6) δ 12.78 (s, 1 H), 12.50 (s, 1 H), 9.07 (s, 1 H), 8.90 (d, 1 H, *J* = 7.4 Hz), 8.46 (d, 1 H, *J* = 7.0 Hz), 7.81 (d, 1 H, *J* = 8.4 Hz), 7.79 (d, 1 H, *J* = 8.2 Hz), 7.72 (t, 1 H, *J* = 7.0 Hz), 7.59 (t, 1 H, *J* = 8.0 Hz), 7.48 (t, 1 H, *J* = 7.4 Hz); exact mass calcd for $C_{17}H_{11}N_3$ 257.0953, found 257.0933. Anal. Calcd for $C_{17}H_{11}N_3 \cdot 1{}^1/_8H_2O$: C, 73.55; H, 4.81; N, 15.14. Found: C, 73.45; H, 4.37; N, 14.89.

3-Chloro-7,12-dihydropyrido[3,2-*b*:5,4-*b'*]diindole (18b): 68%; mp >350 °C; IR (KBr) 3440, 3150, 2800, 1620, 1470 cm^{-1}; MS (CI, CH_4), *m/e* 292 (M + 1); ^{1}H NMR (DMSO-d_6) δ 12.41 (s, 1 H) 12.13 (s, 1 H), 8.92 (s, 1 H), 8.76 (d, 1 H, *J* = 7.9 Hz), 8.20 (d, 1 H, *J* = 2.0 Hz), 7.71 (d, 1 H, *J* = 8.6 Hz), 7.36 (t, 1 H, *J* = 7.2 Hz); exact mass calcd for $C_{17}H_{10}N_3Cl$ 291.0563, found 291.0548. Anal. Calcd for $C_{17}H_{10}N_3Cl$: C, 69.99; H, 3.43; N, 14.41. Found: C, 69.90; H, 3.44; N, 14.41.

Reaction of Phenylhydrazones 20a–d in Ethanolic Hydrogen Chloride. The phenylhydrazones **20a–d** were generated in situ by dissolving **1b** (0.5 g, 1.7 mmol) and the appropriately substituted phenylhydrazine (3.4 mmol) in dry ethanol (5 mL). Two drops of HCl (concentrated) was added to the ethanolic solution and the mixture held at reflux for 20 min. After conversion to the phenylhydrazone was complete, a saturated solution of ethanolic hydrogen chloride (15 mL) was added to the phenylhydrazone solution and the mixture held at reflux overnight. The reaction mixture was then cooled to room temperature and the solvent removed in vacuo to give an oil. The pyridodiindole derivatives **18a,b,d**, individually, were then precipitated as the hydrochloride salts by addition of cold methanol. The solid was filtered and the filtrate concentrated to an oil. The oil was then crystallized from dry ethanol to give the 4-amino-β-carboline dihydrochloride. The pyridodiindole hydrochloride salts (**18a–d**) and 4-amino-β-carboline dihydrochloride could be purified by multiple recrystallizations from ethanol.

3-Methoxy-7,12-dihydropyrido[3,2-*b*:5,4-*b'*]diindole (18d): mp >350 °C (HCl salt); MS (CI, CH_4), *m/e* 288 (M + 1); ^{1}H NMR (DMSO-d_6) δ 12.96 (s, 1 H), 12.72 (s, 1 H), 9.16 (s, 1 H), 8.94 (d, 1 H, *J* = 7.9 Hz), 8.16 (d, 1 H, *J* = 2.0 Hz), 7.85 (d, 1 H, *J* = 8.2 Hz), 7.76 (t, 1 H, *J* = 9.2 Hz), 7.51 (t, 1 H, *J* = 7.5 Hz), 7.28 (d, 1 H, *J* = 8.9 Hz), 3.89 (s, 3 H); exact mass calcd for $C_{18}H_{13}N_3O$ 287.1058, found 287.1040; Anal. Calcd for $C_{18}H_{13}N_3O \cdot HCl \cdot {}^1/_4H_2O$:

(7) It has been suggested by a reviewer that the amination–oxidation reaction resembles the Semmler–Wolff aromatization reaction. [For a review of the Semmler–Wolff reaction see: Watnick, C. Ph.D. Thesis, Seton Hall University, 1970. See also: El-Sheikh, M. I.; Cook, J. M. *J. Org. Chem.* **1980**, *45*, 2585 and references cited therein.] While some analogy to the Semmler–Wolff process is evident, the requirement for the presence of an acidic hydrogen in the ring undergoing oxidation in the amination–oxidation reaction differentiates it from the Semmler–Wolff sequence. Moreover, the reaction conditions (Ac_2O, HOAc, HCl) required to convert the oxime of **1b** into 4-amino-β-carboline (**2b**) would be prohibitive. The acetic anhydride would transform the piperidine NH function (ring C) of **1b** into the corresponding amide and retard the oxidation of this system. The reaction would suffer an analogous fate under modified Semmler–Wolff conditions [CF_3CO_2H, $(CF_3CO)_2O$, HCl]. See: Chang, J.-C.; El-Sheikh, M. I.; Cook, J. M. *Heterocycles* **1979**, *12*, 903.

C, 65.85; H, 4.41; N, 12.80. Found: C, 65.70; H, 4.57; N, 12.69.

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Registry No. **1a**, 75314-80-6; **1b**, 98263-41-3; **2a**, 83478-57-3; **2b**, 98263-44-6; **2b**·2HCl, 109864-52-0; **6**, 67902-64-1; **7**, 98263-36-6; **7**·HCl, 109864-47-3; **8**, 98263-37-7; **11**, 15128-52-6; **12**, 95955-94-5; **13**, 6116-76-3; **14**, 98263-35-5; **15**, 13414-95-4; **16**, 98263-33-3; **17**, 98263-34-4; **18a**, 98263-45-7; **18b**, 106252-03-3; **18d**, 106252-04-4; **19**, 98263-40-2; **20a**, 109864-48-4; **20b**, 109864-49-5; **20c**, 109864-50-8; **20d**, 109864-51-9; **20d**·HCl, 109864-53-1; phenylhydrazine, 100-63-0; (*p*-chlorophenyl)hydrazine, 1073-69-4; (*p*-nitrophenyl)hydrazine, 100-16-3; (*p*-methoxyphenyl)hydrazine, 3471-32-7.

Formation of 1,3-Diynes, 1,3-Dienes, and Biphenyls via the Copper(II) Nitrate Mediated Coupling of Organotin Compounds

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A method for the preparation of symmetrically substituted 1,3-diynes, 1,3-dienes, and biphenyls based on the copper(II) nitrate mediated coupling of organotin compounds **1** (R = alkynyl, alkenyl, aryl) is described. The addition of alkynylstannane **1a**, **1b**, or **1c** (**a**, R = THPOCH$_2$C≡C; **b**, R = *n*-C$_4$H$_9$C≡C: **c**, R = C$_6$H$_5$C≡C) to 1 equiv of Cu(NO$_3$)$_2$·3H$_2$O in THF at 23 °C afforded 1,3-diynes **2a-c** in 85%, 60%, and 50% yield, respectively. Similar treatment of alkenylstannanes **1d**, **1e**, **1f**, or **1g** (**d**, R = O(CH$_2$)$_3$CH=C; **e**, (*E*)-PhCH$_2$OCH$_2$CH=CH; **f**, (*Z*)-PhCH$_2$OCH$_2$CH=CH; **g**, 3,4-(CH$_3$O)$_2$C$_6$H$_3$C(=CH$_2$)) afford the 1,3-dienes **2d-g** in 80%, 72%, 75%, and 71% yield, respectively. In the case of (*E*)- or (*Z*)-vinylstannanes, the dimerization process is found to be highly stereospecific. For example, copper(II) nitrate induced coupling of **1f** (R = (*Z*)-PhCH$_2$OCH$_2$CH=CH) afforded a 23:1 ratio of (*Z,Z*)/(*E,Z*)-diene stereochemistry for **2f** (R = PhCH$_2$OCH$_2$CH=CH). Also prepared by this method were the substituted biphenyls **2h-k** (**h**, R = 4-CH$_3$C$_6$H$_4$; **i**, R = 4-CH$_3$OC$_6$H$_4$; **j**, R = 2-CH$_3$OC$_6$H$_4$; **k**, R = 4-(CH$_3$)-2,6-(CH$_3$O)$_2$C$_6$H$_3$) in 14-66% yield. Aspects about the possible mechanism of dimerization are discussed.

The oxidative dimerization of terminal alkynes to symmetrical diynes (the Glaser[1] and Eglinton[2] reactions) is a classical synthetic reaction which has recently emerged as a cornerstone transformation in the synthesis of several macrocyclic cage compounds that are capable of accomodating organic guest molecules with a high degree of selectivity binding.[3] The fundamental process for the coupling of terminal alkynes is mediated by copper(II) salts ($CuCl_2$ or $Cu(OAc)_2$), in basic media (pyridine or TMEDA), although, this general strategy has undergone numerous alterations in specific experimental conditions. The yields of diynes vary considerably as a function of substrate structure, choice of copper(II) complexes, reaction solvent and temperature.[4] An exception to the copper-mediated method is the recent Pd(II)-catalyzed coupling of alkynes,[5] but this method is limited to the dimerization of *aryl*acetylenes.

We report a new and versatile variation on this transformation leading to good yields of symmetrically coupled products under mild conditions in short reaction times using copper(II) nitrate with the corresponding alkynylstannanes according to eq 1. An especially interesting discovery is the applicability of this procedure to the dimerization of *vinyl*- and *aryl*stannanes.

$$\underset{\mathbf{1}}{\mathrm{RSn}(n\text{-}\mathrm{C_4H_9})_3} \xrightarrow{\mathrm{Cu(NO_3)_2{\cdot}3H_2O}} \underset{\mathbf{2}}{\mathrm{R{-}R}} \qquad (1)$$

R = alkynyl, alkenyl, aryl

Results and Discussion

Coupling of Alkynylstannanes: Preparation of 1,3-Diynes. The addition of neat alkynylstannane **1a** (cf. Table I) to a solution of 1 equiv of Cu(NO$_3$)$_2$·3H$_2$O in tetrahydrofuran at 23 °C gave, after 10 min, the symmetrical diyne **2a** in 85% isolated yield (see eq 2). By con-

$$\underset{\mathbf{1a-c}}{\mathrm{RC{\equiv}CSnBu_3}} \xrightarrow{\mathrm{Cu(NO_3)_2{\cdot}3H_2O}} \underset{\mathbf{2a-c}}{\mathrm{RC{\equiv}CC{\equiv}CR}} \qquad (2)$$

trast, the Glaser-type coupling of the corresponding alkyne, 3-(tetrahydro-2*H*-pyran-2-yloxy)-1-propyne,[6] with either $CuCl/O_2$ or $Cu(OAc)_2$ in TMEDA at 40 °C for 5 h afforded, at best, a 34% yield of diyne **2a**. Surprisingly, alkynylstannane **1a** was inert toward $Cu(OAc)_2$, $CuCl_2$, $CuBr_2$, and $CuSO_4$ under similar conditions. However, dimerization using $AgNO_3$[7] gave results identical with those from the Cu(NO$_3$)$_2$-mediated coupling. Brief studies using Cu(NO$_3$)$_2$ and alkynylstannane **1a** showed that a variety of nonaqueous solvents (DME, DMF, dioxane, acetone, methanol) were suitable for the coupling reaction, but no reaction was

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