2-Benzazepines. 8.[1] Zerovalent Nickel Mediated Biaryl Synthesis of an Anxiolytic Pyrimido[5,4-*d*][2]benzazepine

David L. Coffen,* Beatrice Schaer, Fred T. Bizzarro, and Julia B. Cheung

Research and Development Division, Hoffmann-La Roche Inc., Nutley, New Jersey 07110

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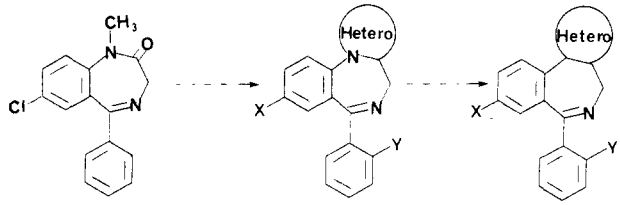
9-Chloro-7-(2-chlorophenyl)pyrimido[5,4-*d*][2]benzazepine, a potent anxiolytic agent, was synthesized in three steps from 4-chloro-5-methylpyrimidine and 2-iodo-2',5-dichlorobenzophenone In the key step these materials were coupled in an unsymmetrical biaryl synthesis mediated with zerovalent nickel. The methyl group of the resulting product was brominated with NBS, and the seven-membered ring was closed with ammonia. Three byproducts of the coupling reaction were isolated and characterized. They proved to be 5,5'-dimethyl-4,4'-bipyrimidinyl, 4,4'-dichloro-2,2'-bis(*o*-chlorobenzoyl)biphenyl, and 2-chloro-9-fluorenone. An improved procedure for the Sandmeyer conversion of aminobenzophenones to iodobenzophenones is also described. Under conditions for palladium-catalyzed coupling of the ketone with terminal acetylenes, the oximes of 2-iodo-2',5-dichlorobenzophenone undergo cyclization to a 1,2-benzisoxazole or reductive loss of iodine, depending on whether the *Z* or *E* oxime is used.

The systematic variation and elaboration of the diazepam structure (1) has been and continues to be one of

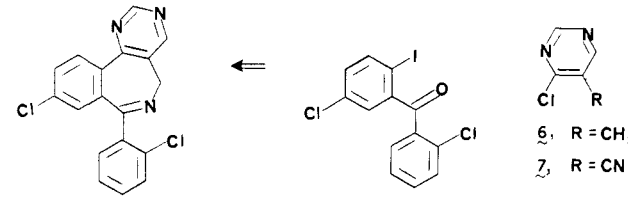


1 2 3

the most active areas of research in the chemistry of CNS agents.[2] A particularly fruitful avenue of investigation led to compounds of type **2** in which an additional heterocyclic ring is a fused to the 1,4-benzodiazepine.[3] Clinically important imidazo- and triazolobenzodiazepines emerged from this class.[4]

Further evolution of this genus was pursued by Trybulski,[5] Gschwend,[6] and their respective co-workers and led to the discovery that compounds of type **3** continued to exhibit the characteristic CNS pharmacology of 1,4-benzodiazepines, even though they lack a nitrogen atom at the 1-position. This discovery certainly has implications which bear on structure/activity considerations and the nature of the benzodiazepine receptor sites. However, a consequence of particular interest to synthetic chemists is that the traditional methods of benzodiazepine synthesis[7] are not applicable to compounds of type **3**. New approaches are required, and the opportunity of applying some of the more recent advances in organic synthesis is offered, as is elegantly demonstrated in papers by Trybulski[5] and Gschwend.[6]

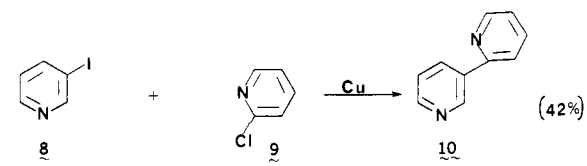
The present investigation was focussed on compound **4** which, because of its promising pharmacological profile,[5] was selected for clinical study.



4 5

With the degree of convergence as a criterion, a synthesis scheme based on the Ullmann-type coupling of **5** and **6** (or **7**) is clearly attractive. Moreover, favorable literature precedents, both conceptual[6] and empirical,[8,9] existed for such a scheme.

Halopyrimidines have been converted to bipyrimidinyls by using the Ullmann biaryl synthesis,[8] and the prognosis for unsymmetrical coupling of **5** and **6** was good in view of the reported results with **8** and **9**.[9]



8 9 10

An equally propitious consideration was the current status of the Ullmann reaction. Although known for at least 82 years,[10] this reaction has received a great deal of attention in recent years, resulting in substantially improved procedures for carrying it out.[11] The method developed by Semmelhack and co-workers,[12] which utilizes

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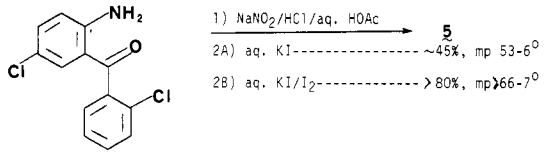
zerovalent nickel compounds instead of copper powder, is particularly advantageous because of the improved yields and lower reaction temperatures.

Semmelhack's reaction was applied in its original form to the coupling of **5** and **6**, even though the use of air-sensitive zerovalent nickel compounds in stoichiometric amounts would pose a serious scale-up problem. This drawback has been largely overcome by subsequent developments wherein the nickel compounds are used catalytically or are generated in situ.[13]

Results and Discussion

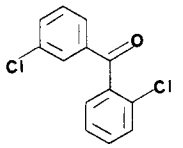
The iodobenzophenone **5** is a known compound[5] and was prepared by applying the appropriate Sandmeyer reaction to commercially available 2-amino-2',5-dichlorobenzophenone (**11**). The published procedure entailed the



11

precipitation and collection of the diazonium compound as its tetrafluoroborate. In order to avoid the potential hazard of this operation and to improve the yield, we ran the entire Sandmeyer sequence in an aqueous acetic acid solution. However, both the yield and the quality of the product obtained with this modification were unsatisfactory (step 2A).

A major byproduct with very similar R_f on TLC was isolated by column chromatography and identified spectroscopically (IR, NMR, MS) as the reduction product **12**.

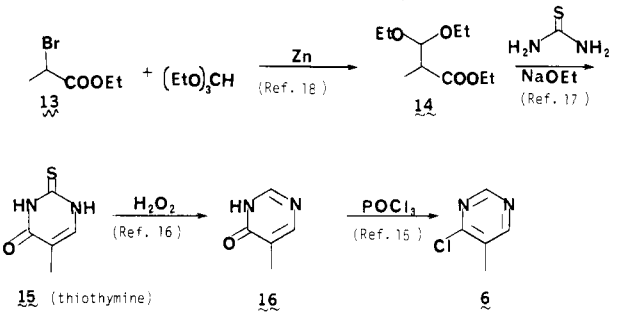


12

Reasoning, perhaps fallaciously,[14] that the pathway to **12** included a one-electron transfer step from I^- to the diazonium ion, we evaluated the effect of added I_2 on the amount of **12** formed (step 2B). This worked extremely well. Both the yield and quality of **5** were excellent when 0.5 equiv of iodine was dissolved in the KI solution before it was added to the diazonium ion solution. The same salutary effect has been found in other Sandmeyer reactions involving the replacement of NH_2 by I on substrates bearing electron-withdrawing groups.

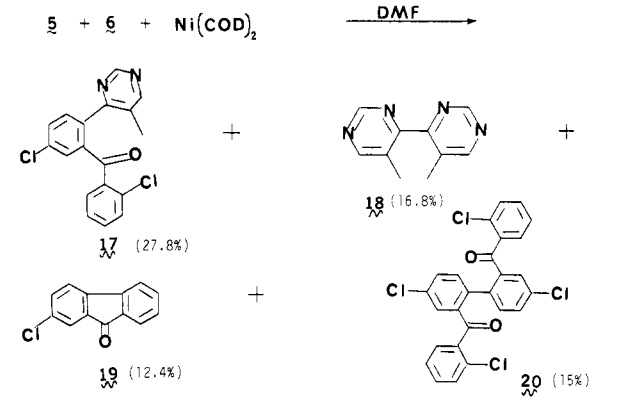
The 4-chloro-5-methylpyrimidine (**6**) required is also a known compound, readily obtained from 4-hydroxy-5-methylpyrimidine (**16**) by treatment with $POCl_3$.[14] At first **16** was obtained from the condensation of formamidine acetate and ethyl α-formylpropionate. However, the yield was poor and the isolation awkward. The oxidative desulfurization of thiothymine (**15**)[16] was found to be a much

Scheme I



better method and was incorporated as shown in Scheme I.

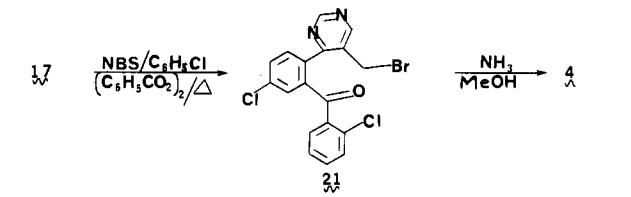
The coupling of **5** and **6** was carried out by using the procedure reported by Semmelhack.[12] Thin-layer chromatographic analysis of the crude product mixture revealed at once that several products were formed. These were isolated by column chromatography and characterizied as compounds **17**–**20**.



The yields shown are based on moles of product per mole of $Ni(COD)_2$ and are calculated in this way to reflect the relative efficiencies of the four main reaction pathways. The isolated yields of **18** and **20** based on **6** and **5**, respectively, would be 33.6% and 30%, respectively. The possibility of forming trimers etc. may also account for some of the material (72 mol % is accounted for).

The 2:1:1 distribution of the unsymmetrical and the two symmetrical coupling products suggests that compounds **5** and **6** have comparable reactivity as partners in the $Ni(COD)_2$-mediated biaryl synthesis. The results are skewed somewhat by the unexpected efficiency of the intramolecular reaction leading to **19** (cf. ref 12).

Completion of the synthesis was straightforward. Compound **17** was subjected to free-radical bromination with NBS, and the resulting bromomethyl compound **21**



was treated with ammonia in methanol, effecting cyclization to **4**. Both reactions proceeded in high yield, although the optimum yield of **21** was obtained at ~40% conversion.

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(14) The oxidation potentials of I_3^- and I^- are almost too close (−0.5338 vs. −0.535 V) to rationalize the observed effect in this way.

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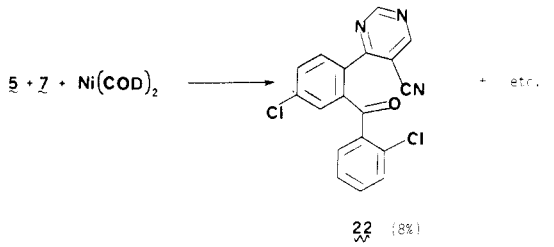
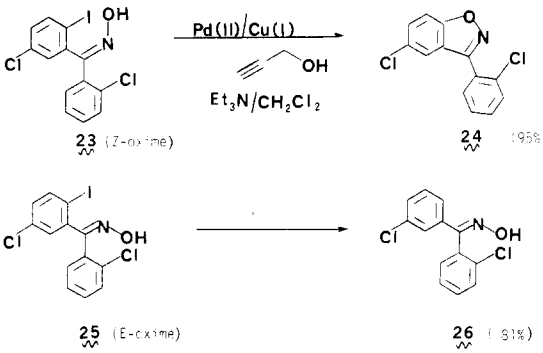
At the planning stage it was clear that an even more direct synthesis of **4** could be devised in which the substituent at the 5-position on the pyrimidine ring included a nitrogen atom. With this in mind the known[19] pyrimidine **7** was prepared and coupled with **5** by using $Ni(COD)_2$ in DMF.



22 (8%)

This approach had two disadvantages in the poor stability of **7** and low yield of **22**. In addition, we were unable to carry out a selective reduction of the nitrile group in **22**.

The original synthesis[5] of compound **4** entailed the palladium-catalyzed coupling of **5** with a monosubstituted acetylene.[20] Within this context the coupling reactions of the *E* and *Z* oximes of **5** with propargyl alcohol were also investigated with the results shown below.



23 (Z-oxime) 24 (95%)

25 (E-oxime) 26 (91%)

The oxime group effectively blocks the coupling reaction in a manner that depends on the configuration about the C=N bond. The species oxidized in the reduction to form **26** is probably propargyl alcohol.

The *Z* oxime **23** is the major product in the reaction of **5** with hydroxylamine hydrochloride in boiling pyridine (Scheme II). Fractional crystallization afforded a pure sample.

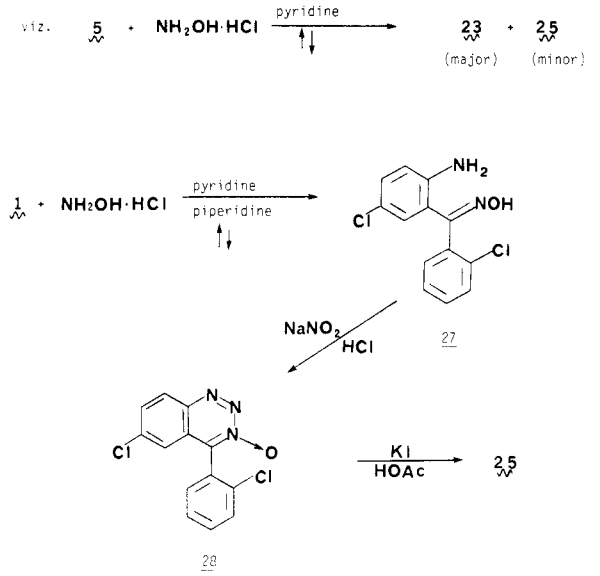
The *E* oxime **25** was prepared by a stereospecific synthesis, which also served to confirm the *E* and *Z* assignments (cf. ref 21).

Experimental Section

Melting points are uncorrected. NMR spectra were recorded on a Varian XL-100 instrument and are reported in parts per million from internal Me_4Si. Elemental analyses were carried out in our Microanalytical Laboratory under the direction of Dr. F. Scheidl.

2′,5-Dichloro-2-iodobenzophenone (5).[22] Into each of two 22-L flasks equipped with mechanical stirrers, thermometers and dropping funnels topped with gas bubblers were placed 675 g (2.535 mol) of 2-amino-2′,5-dichlorobenzophenone and 1.26 L of

Scheme II



glacial acetic acid. To each of the stirred mixtures was added 504 mL of concentrated hydrochloric acid. The mixtures were stirred for 1.0 h to effect solution, cooled to 10 °C with an ice–water bath, and treated with a solution of 185 g (2.681 mol) of $NaNO_2$ in 882 mL of deionized H_2O over 0.75 h at a rate such that the temperature remained less than 20 °C. The mixtures were stirred for 0.5 h with continued cooling. To each flask were then added 2.52 L of cold (less than 10 °C) deionized H_2O and 5.04 L of cold (less than 10 °C) ethyl acetate. A solution of 504 g (3.035 mol) of KI and 378 g (1.489 mol) of I_2 in 2.52 L of deionized H_2O was added to each flask over 1.5 h at a rate such that the temperature was kept less than 15 °C. The mixtures were stirred at 5–15 °C for 2.5 h (N_2 evolution during addition and for ca. 1.0 h thereafter) and stored at 3 °C overnight (for convenience only). The aqueous phase of the combined mixtures was extracted with ethyl acetate (2 × 2.0 L and 2 × 1.0 L). The combined mixture of the organic phase and extracts was washed with a solution of 1.896 kg (7.639 mol) of $Na_2S_2O_3·5H_2O$ in 7.68 L of deionized H_2O, with saturated $NaHCO_3$ (3 × 4.0 L, last wash basic), and with 4.0 L of brine and dried over Na_2SO_4. The solvent was removed on a rotary evaporator at 40 °C to a volume of ca. 2.5 L. This brown oil was stirred and cooled in an ice–water bath for 0.75 h. The solid was collected by filtration on coarse sintered glass, washed with cold (−70 °C) ethyl acetate (2 × 400 mL), and dried in a forced-air oven at 40 °C to give 1.304 kg of **5** as a yellow powder, mp 68–70 °C (lit.[4] mp 64–66 °C). Concentration of the mother liquors and washings gave two additional crops of product: crop 2, 296 g, mp 67–70 °C; crop 3, 109 g, mp 66–69 °C. The three crops (total 1.709 kg, 89% yield) were combined for further use.

Ethyl 3,3-Diethoxy-2-methylpropionate (14). The Reformatsky reaction of ethyl 2-bromopropionate and triethyl orthoformate was carried out as described by Deno[18] and by Kupiecki and Coon[18] with two modifications. Toluene was used instead of benzene as the solvent, and a toluene solution of the reactants was passed through a vertical column of activated granular zinc maintained at 90 °C, as described by Ruppert and White.[23] A 57% yield of distilled product, having a purity of 96% by GC, was obtained.

Thiothymine (15). This compound was prepared from **14** and thiourea in 48% yield by using the procedure reported by Bennett[17] for the preparation of a radioactive sample.

4-Hydroxy-5-methylpyrimidine (16). The oxidative desulfurization of thiothymine (**15**) with H_2O_2 was carried out in the manner reported by Williams, Ruehle, and Finkelstein.[16] Desulfurization with Raney nickel was also reported.[15]

4-Chloro-5-methylpyrimidine (6). Compound **16** was treated with $POCl_3$ and worked up as described by Vanderhaeghe and Claesen[15] to give **6** in 81% yield.

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(22) The experiment described was carried out by Gary Siwruk in the Kilo Laboratory.
(23) Ruppert, J. F.; White, J. D. *J. Org. Chem.* **1974**, *39*, 269.

2',5-Dichloro-2-(5-methyl-4-pyrimidinyl)benzophenone (17) and Other Products (18–20) Produced in the Coupling of 5 and 6. The coupling reactions were carried out by combining the reagents in a dry box and then allowing them to proceed under an argon atmosphere. To a solution of 4.1 g (0.015 mol) of Ni(COD)$_2$ in 40 mL of DMF was added a solution of 1.75 g (0.0136 mol) of 4-chloro-5-methylpyrimidine (**6**) in 20 mL of DMF. Half of a solution of 4.88 g (0.0129 mol) of 2-iodo-2',5-dichlorobenzophenone (**5**) in 20 mL of DMF was added, and the temperature was raised to 40 °C. The remainder of the solution was added dropwise over 2 h. The mixture was stirred at 40 °C for 2 days. It was then quenched into 1 N HCl and extracted with methylene chloride. After drying and evaporation of the solvent, 4.3 g of crude product mixture was obtained as a yellow solid. The four products in this mixture were separated by chromatography on silica gel by using a cominbation of column and thick-layer methods with hexane/ethyl acetate as the eluents. In order of elution there was obtained the following. **2-Chloro-9-fluorenone (19)**: 0.358 g; mp 121–123 °C (lit. mp 125 °C); identified by its NMR and mass spectra. Anal. Calcd for $C_{13}H_7ClO$: C, 72.74; H, 3.29; Cl, 16.52. Found: C, 72.42; H, 3.08; Cl, 16.57.

2,2'-Bis(*o*-chlorobenzoyl)-4,4'-dichlorobiphenyl (20): colorless crystals (from ether/hexane); 1.013 g; mp 177–178 °C; IR ($CHCl_3$) 1680 cm^{-1}; mass spectrum, *m/e* 359 ($M^+ - ClC_6H_4CO$); ^1H NMR ($CDCl_3$) 7.1–7.5 (aromatic). Anal. Calcd for $C_{26}H_{14}Cl_4O_2$: C, 62.43; H, 2.82; Cl, 28.35. Found: C, 62.42; H, 2.83; Cl, 28.55.

17: 1.29 g; colorless crystals (from hexane); mp 104–105 °C; IR (KBr) 1670 cm^{-1}; mass spectrum, *m/e* 342 (M^+); ^1H NMR ($CDCl_3$) 2.17 (s, 3 H), 7.2–7.7 (m, 7 H), 8.44 (s, 1 H), 8.91 (s, 1 H). Anal. Calcd for $C_{18}H_{12}Cl_2N_2O$: C, 62.99; H, 3.52; Cl, 20.66; N, 8.16. Found: C, 62.85; H, 3.75; Cl, 20.69; N, 8.21.

5,5'-Dimethyl-4,4'-bipyrimidinyl (18): 0.422 g; colorless crystals; mp 143–145 °C; mass spectrum, *m/e* 186 (M^+); ^1H NMR ($CDCl_3$) 2.26 (s, 6 H), 8.76 (s, 2 H), 9.16 (s, 2 H). Anal. Calcd for $C_{10}H_{10}N_4$: C, 64.50; H, 5.41; N, 30.09. Found: C, 64.68; H, 5.41; N, 29.87.

2',5-Dichloro-2-[5-(bromomethyl)-4-pyrimidinyl]benzophenone (21). A mixture of compound **17** (1.015 g, 0.003 mol), *N*-bromosuccinimide (0.580 g, 0.0035 mol), and benzoyl peroxide (59 mg) in 84 mL of chlorobenzene was heated to reflux under argon for 24 h. The solvent was removed under vacuum, and the residue was chromatographed on 30 g of silica gel. The product was eluted with 1:1 hexane/ethyl acetate, and recovered starting material (0.621 g) was eluted with ethyl acetate. The yield of **21** was 0.456 g (94% based on starting material consumed). Compound **21** is colorless and crystalline: mp 140–142 °C dec; IR ($CHCl_3$) 1687 cm^{-1}; mass spectrum, *m/e* 420 (M^+); ^1H NMR ($CDCl_3$) 4.32 (s, 2 H), 7.2–7.8 (m, 7 H), 8.75 (s, 1 H), 9.02 (s, 1 H). Anal. Calcd for $C_{18}H_{11}BrCl_2N_2O$: C, 51.22; H, 2.63; Br, 18.93; Cl, 16.80; N, 6.64. Found: C, 50.74; H, 2.58; Br, 18.22; Cl, 16.46; N, 6.29.

9-Chloro-7-(2-chlorophenyl)pyrimido[5,4-*d*][2]benzazepine (4). A mixture of 0.564 g of compound **21**, 20 mL of concentrated aqueous ammonia, 20 mL of methanol, and 5 mL of ethyl acetate was stirred at room temperature for 16 h, during which time a clear solution formed. The residue left on evaporation was taken up in 50 mL of ether, treated with Norite A, filtered through a plug of activated alumina (Type F-20), and evaporated. The resulting product was recrystallized from ether to give **4**: 0.294 g (64.8%); colorless crystals; mp 121–122 °C (lit.[5] mp 122–124 °C); mass spectrum, *m/e* 339 (M^+). Anal. Calcd for $C_{18}H_{11}Cl_2N_3$: C, 63.55; H, 3.26; Cl, 20.84; N, 12.35. Found: C, 63.92; H, 3.20; Cl, 20.85; N, 12.20.

2',5-Dichloro-2-(5-cyano-4-pyrimidinyl)benzophenone (22). A solution in 30 mL of DMF of benzophenone **5** (2.0 g, 0.005 mol), 4-chloro-5-cyanopyrimidine[19] (**7**; 1.0 g, 0.007 mol), and Ni(COD)$_2$ (1.6 g, 0.006 mol) was stirred under argon at 40 °C for 24 h. After the workup with dilute HCl and methylene chloride, the crude product mixture was chromatographed on 30 g of silica gel with 2:1 hexane/ethyl acetate. There was thus obtained 0.16 g (8.5%) of compound **22**. An analytical sample from ether was obtained as off-white crystals: mp 115–116 °C; IR ($CHCl_3$) 2235, 1683 cm^{-1}; mass spectrum, *m/e* 353 (M^+); ^1H NMR ($CDCl_3$) 7.2–7.8 (m, 7 H), 8.94 (s, 1 H), 9.27 (s, 1 H). Anal. Calcd for $C_{18}H_9Cl_2N_3O$: C, 61.04; H, 2.56; Cl, 20.02; N, 11.86. Found: C, 59.95; H, 2.38; Cl, 18.40; N, 11.86.

2',5-Dichloro-2-iodobenzophenone (*Z*)-Oxime (23). A solution of 10 g of the benzophenone **5** and 15 g of hydroxylamine hydrochloride in 125 mL of pyridine was heated at reflux for 21 h. After cooling, the mixture was partitioned between water and ether acetate. The organic layer was washed with dilute HCl and with dilute $NaHCO_3$ solutions. The 11 g of residue obtained after drying and evaporation of solvent was immediately taken up in 20 mL of ether, and the solution was stored in the cold overnight. The crystalline precipitate was collected by filtration, washed with 1:1 ether/hexanes, and air-dried to give 2.9 g of tiny, colorless needles: mp 174–177 °C; IR (Nujol) 3200 cm^{-1}; ^1H NMR ($CDCl_3$/Me_2SO) 7–8 (m, aromatic H); mass spectrum, *m/e* 391 (M^+). Anal. Calcd for $C_{13}H_8Cl_2INO$: C, 39.83; H, 2.06; Cl, 18.09; I, 32.37; N, 3.57. Found: C, 39.67; H, 2.07; Cl, 18.30; I, 32.67; N, 3.31. The mother liquor contained a mixture of the two isomeric oximes, with the one isolated (more polar on TLC) being the major component.

5-Chloro-3-(*o*-chlorophenyl)-1,2-benzisoxazole (24). This compound was obtained in the attempt to couple iodo oxime **23** with propargyl alcohol as follows. A solution was prepared from 2.0 g (0.005 mol) of iodo oxime **23**, 0.64 mL (0.011 mol) of propargyl alcohol, 11 mL of triethylamine, and 12 mL of methylene chloride. The solution was stirred and chilled in an ice/acetone bath, and argon was bubbled through it for 10 min. The catalyst consisting of 40 mg each of cuprous iodide and bis(triphenylphosphine)-palladium(II) chloride was added, the bath was removed, and heat (to reflux) was applied with continued stirring under argon. After 3 h an additional 30 mg of each catalyst component was added. Stirring at reflux was continued for a further 4.5 h. After the mixture cooled, the solvent was evaporated under reduced pressure. The residue was partitioned between methylene chloride and water. The organic layer was washed with dilute HCl and $NaHCO_3$ solutions, dried, and evaporated to give 1.28 g (95%) of crude compound **24** as a tan solid. A sample recrystallized from ether gave colorless needles: mp 100–103 °C; mass spectrum, *m/e* 263 (M^+); ^1H NMR ($CDCl_3$) 7.2–7.7 (m, aromatic H). Anal. Calcd for $C_{13}H_7Cl_2NO$: C, 59.12; H, 2.67; Cl, 26.85; N, 5.30. Found: C, 59.17; H, 2.72; Cl, 26.90; N, 5.35.

2',5-Dichloro-2-aminobenzophenone Oximes (27). A mixture of 26.8 g of hydroxylamine hydrochloride, 34.2 g of 2',5-dichloro-2-aminobenzophenone (**5**), 10 mL of piperidine, and 100 mL of pyridine was heated at reflux for 20 h by using an oil bath kept at 150–170 °C. The solvent was removed under reduced pressure, and the residue was partitioned between water and ether. The organic layer and extracts of the aqueous layer were combined, dried, and evaporated to leave a yellow oil. This material consisted of a mixture of the starting ketone and its two isomeric oximes. Chromatography on a silica gel column with 1:1 hexane/ethyl acetate afforded 19.6 g (57%) of recovered ketone and 9.9 g (27.4%) of mixed oximes **27**. The mixed oximes were used for conversion to benzotriazine **28**. Small amounts of isomerically pure oximes were obtained in chromatography fractions as off-white powders: mp 136–138 °C (more polar) and 147–149 °C (less polar).

6-Chloro-4-(*o*-chlorophenyl)-1,2,3-benzotriazine 3-Oxide (28). A solution of 17.3 g of mixed oximes **27** in 85 mL of ethanol was prepared in a 2-L flask and cooled in an ice bath. To this was added 870 mL of 1 N HCl, giving a colorless precipitate. With continued cooling and stirring, a solution of 7 g of $NaNO_2$ in 300 mL of water was added gradually during 15 min. A yellow precipitate formed. This was collected, washed with water, and dried to give 14.9 g (83%) of **28** as a yellow powder. A sample recrystallized from ether/hexane as a hydrate, mp 139–141 °C. Anal. Calcd for $C_{13}H_7Cl_2N_3O{\cdot}H_2O$: C, 50.35; H, 2.92; Cl, 22.86; N, 13.55. Found: C, 50.42; H, 2.41; Cl, 24.96; N, 13.57.

2',5-Dichloro-2-iodobenzophenone (*E*)-Oxime (25). A mixture of 14.9 g of the benzotriazine **28** and 15 g of KI in 150 mL of acetic anhydride was stirred at room temperature for 2 days. Additional 2-g portions of KI were added after 4 h and after 24 h. The mixture was partitioned between water and ether. The ether extracts were combined, washed with (excess) $NaHCO_3$ solution, filtered through a plug of silica gel, and evaporated to give 17.7 g of crude (*E*)-oxime **25**. Recrystallization from toluene/petroleum ether gave off-white crystals: 11.7 g (58.6%); mp 159–161 °C. The material gave a single spot on TLC corresponding to the minor (less polar) isomer formed in the reaction

of ketone **5** and hydroxylamine. Anal. Calcd for $C_{13}H_8Cl_2INO$: C, 39.83; H, 2.06; Cl, 18.09; I, 32.37; N, 3.57. Found: C, 39.78; H, 2.08; Cl, 18.39; I, 32.58; N, 3.35.

2,3'-Dichlorobenzophenone (*Z*)-Oxime (26). This compound was obtained in the attempt to couple iodo oxime **25** with propargyl alcohol. The coupling experiment was carried out in the manner and on the scale described for the preparation of compound **24**. The crude product was a light brown solid: mp 100–112 °C; 1.1 g (81%). A sample recrystallized from toluene/petroleum ether with charcoal treatment gave colorless crystals: mp 111–113 °C; IR ($CHCl_3$) 3600, 3300, 1595, 1565 cm^{-1}; mass spectrum, *m/e* 265 (M^+); ^1H NMR ($CDCl_3$) 7.2–7.6 (m, aromatic H), 9.1 (br s, OH). Anal. Calcd for $C_{13}H_9Cl_2NO$: C, 58.67; H, 3.41; Cl, 26.64; N, 5.16. Found: C, 58.86; H, 3.40; Cl, 26.82; N, 5.28.

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Registry No. **4**, 76988-39-1; **5**, 76049-50-8; **6**, 51957-32-5; **7**, 16357-68-9; **14**, 36056-90-3; **15**, 636-26-0; **16**, 17758-52-0; **17**, 87999-60-8; **18**, 87999-62-0; **19**, 3096-47-7; **20**, 87999-61-9; **21**, 87999-63-1; **22**, 87999-64-2; (*Z*)-**23**, 87999-65-3; **24**, 87999-66-4; (*E*)-**25**, 87999-68-6; (*Z*)-**26**, 87999-69-7; (*Z*)-**27**, 24048-12-2; (*E*)-**27**, 34609-76-2; **28**, 87999-67-5; $Ni(COD)_2$, 1295-35-8; 2-amino-2',5-dichlorobenzophenone, 2958-36-3; ethyl 2-bromopropionate, 535-11-5; triethyl orthoformate, 122-51-0; thiourea, 62-56-6; propargyl alcohol, 107-19-7; cuprous iodide, 7681-65-4; bis(triphenylphosphine)palladium(II) chloride, 13965-03-2.

Efficient Synthesis of Pyrrolizidine and Indolizidine Alkaloids Utilizing Anodically Prepared α-Methoxy Carbamates as Key Intermediates[1]

Tatsuya Shono,* Yoshihiro Matsumura, Kenshi Uchida, Kenji Tsubata, and Atsushi Makino

Department of Synthetic Chemistry, Faculty of Engineering, Kyoto University, Yoshida, Sakyo, Kyoto 606, Japan

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Pyrrolizidine and indolizidine skeletons were constructed effectively by 1,2-annulation on a pyrrolidine ring by utilizing anodically prepared 1-(alkoxycarbonyl)-2-methoxypyrrolidines as key intermediates. *Elaeocarpus* alkaloids (±)-elaeokanine A and (±)-elaeokanine C were synthesized in five steps from 1-(methoxycarbonyl)-2-methoxypyrrolidine, and also the synthesis of necins of *Senecio* alkaloids (±)-trachelanthamidine and (±)-isoretronecanol was achieved in six steps from 1-(benzyloxycarbonyl)-2-methoxypyrrolidine.

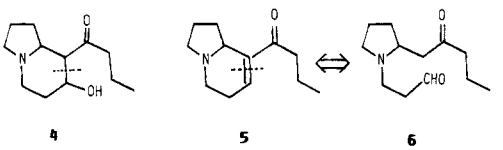
The alkaloids containing a pyrrolizidine **1** or an indolizidine **2** skeleton have been widely found in plants and hence attracted much attention as the targets of organic synthesis.[2]

1 **2**

Although a variety of synthetic methods[3] for constructing such skeletons have been exploited so far, it is worthwhile to exploit new methods starting from easily accessible compounds.

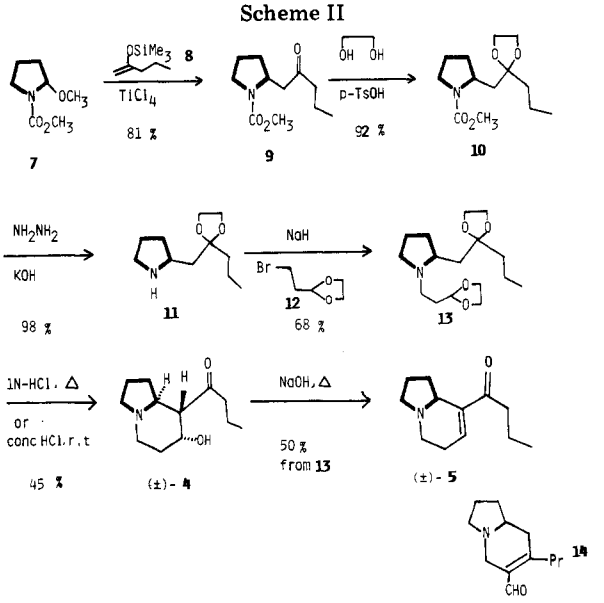
Since we have already found versatile methods of carbon–carbon bond formation[4,5] at the α-position of pyrrolidine utilizing anodically α-methoxylated *N*-(methoxycarbonyl)pyrrolidine[7] as the key starting compound, we have successfully applied these methods to the synthesis of skeletons **1** and **2** as exemplified in the present study by the synthesis of *Elaeocarpus* alkaloids (±)-elaeokanine A and (±)-elaeokanine C and the necins of *Senecio* alka-

Scheme I



4 **5** **6**

Scheme II



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