Chemistry of Heterocyclic Compounds. 36. Reduction Reactions of Pyridyl Ketones with Low Valent Titanium Reagents

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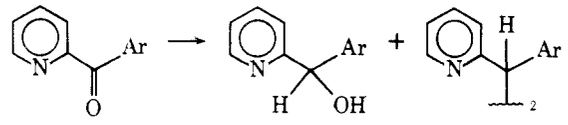
Pyridyl ketones react with low valent titanium reagents, generated either by $LiAlH_4$ and $TiCl_3$ or Na^0 and $TiCl_3$, to give either the corresponding alcohol or the reductively coupled products. The olefinic products generally arise when intramolecular N-complexation of the titanium ions is prevented, and ill-defined polymeric material is formed when two sites of potential complexation are available.

Recently, intermolecular reductive coupling of aldehydes and ketones to olefins has been accomplished by the use of low valent titanium reagents which were generated from titanium trichloride with either lithium aluminum hydride[2] or a reactive metal,[3] such as Zn, Mg, or Li. In general to the best of our knowledge, all cases of reductive coupling, via this procedure, have been limited to aromatic or aliphatic ketones and aldehydes; few, if any, heterocyclic carbonyl compounds have been utilized. We herein report the reaction of pyridyl ketones with low valent titanium reagents.

Both tetraphenylethene[2a] and bis(fluorenylidene)[2a] have been successfully prepared in our hands from the corresponding ketones in excess of 85% yield by either method a ($LiAlH_4$–$TiCl_3$)[2a] or b (Na^0–$TiCl_3$).[3] Treatment of phenyl 2-pyridyl ketone (**1a**) under method a conditions afforded (93%) phenyl(2-pyridyl)methanol (**2a**) and, in low yields (ca. 5%), the reduced coupled compound **3a**. The mass spectral

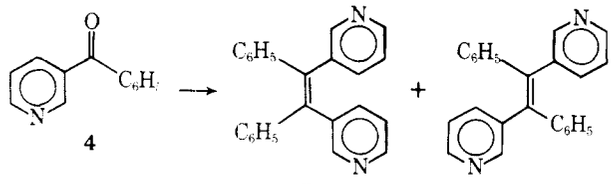


1a, Ar = C_6H_5
b, Ar = 2-pyr

2 **3**

data of **3a** indicated a weak parent ion (*m/e* 336; 28%) and formation of a very intense *m/e* 168 peak ($C_{12}H_{10}N$, 100%) due to the facile fragmentation of the central bis(benzylic) bond. NMR spectral data of **3a** showed a singlet at δ 5.31 for the nonexchangeable benzylic hydrogens and a complex aromatic region, which is not indicative of the expected rigid tetrasubstituted ethenes. Di-2-pyridyl ketone (**1b**) similarly gave the corresponding alcohol **2b**, which upon prolonged contact with air underwent easy oxidation to both starting **1b** and several minor uncharacterized products. Reduction, via method b, of **1b** afforded only the carbonyl reduced product **2b** along with unchanged starting material.

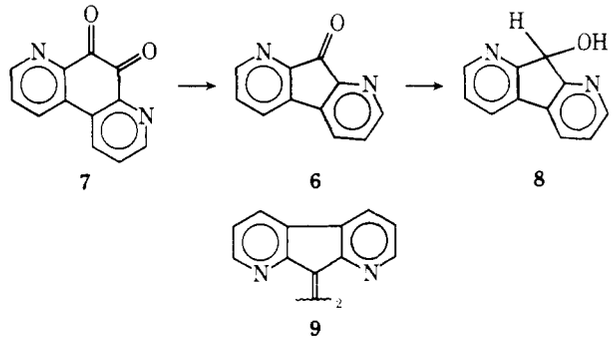
3-Benzoylpyridine (**4**), when treated with $TiCl_3$–$LiAlH_4$ in THF (method a), gave the desired isomeric coupled olefins (*E*)-**5** and (*Z*)-**5**, as well as unchanged starting material. Mass spectral data for **5** showed an intense parent ion (*m/e* 334, 100%) and both possessed near superimposible fragmentation patterns. The NMR spectral data of (*Z*)-**5** and (*E*)-**5** indicated the unique 2,6-pyridyl hydrogens, an upfield shift of the *o*-phenyl hydrogen (compared to **4**), and a complex aromatic



4 (*Z*)-**5** (*E*)-**5**

region. Eu-shift studies were conducted on both isomers in order to ascertain their configurations (Figures 1 and 2). At 21% Eu-shift reagent [Eu(fod)$_3$], the 5-ppm downfield shift of the 2,6-pyridyl hydrogens confirmed that the shift reagent is complexed with the pyridyl nitrogen atom(s). The near first-order spectrum and decoupling experiments indicated that the 199–200 °C melting isomer possesses the *Z* configuration.

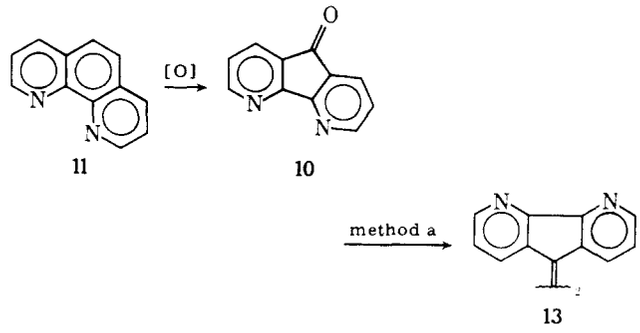
1,8-Diazafluorenone (**6**) was synthesized from 4,7-phenanthroline-5,6-dione (**7**),[4] according to the procedure of Druey and Schmidt.[5a] This oxidative ring contraction was accomplished by treatment of **7** with dilute hydroxide ion in the presence of air; a black polymeric insoluble material, whose structure was not ascertained, was also isolated.[6] Treatment of **6** with $TiCl_3$–$LiAlH_4$ (method a) in THF resulted in the predominant formation of an insoluble black solid, similar to that above, along with unchanged starting material and traces (1%) of a reduced compound (mp 143 °C). Sodium borohydride reduction of **6** afforded an authentic sample of **8**, which confirmed that the compound melting at 143 °C was not alcohol **8**. Due to limited quantities further structural analysis was not conducted. Schonberg and Junghans synthesized bis(1,8-diazafluorenylidene) (**9**) by the UV-induced coupling of **6** and 1,8-diazafluorene to give the intermediate alcohol, which was dehydrated to afford **9** in unspecified yields.[7]



7 **6** **8**

9

4,5-Diazafluorenone (**10**) was isolated as the major byproduct in the oxidation of 1,10-phenanthroline (**11**), according to the procedure of Eckard and Summers.[8] Ketone **10** exists almost exclusively as a hydrate, which can be dehydrated, only with difficulty, by sublimation in vacuo at elevated temperatures or better by treatment with calcium hydride immedi-



11 **10**

13

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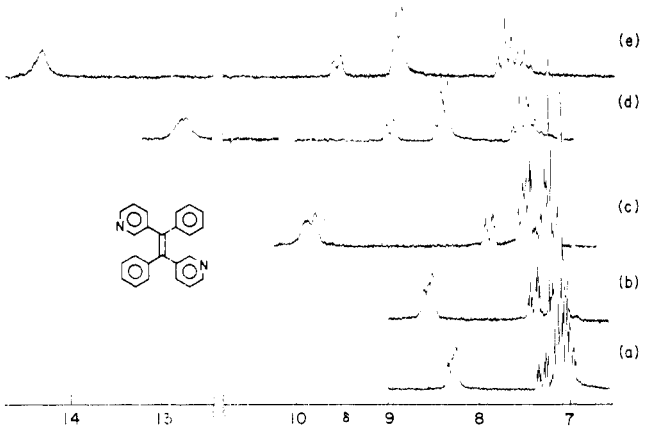


Figure 1. ^{1}H NMR (100 MHz) spectra of (*E*)-**5** at 30 °C in $CDCl_3$ solution containing the substrate (0.16 M) at various mole ratios of Eu(fod)$_3$: (a) 0%; (b) 1%; (c) 5%; (d) 11%; (e) 21%.

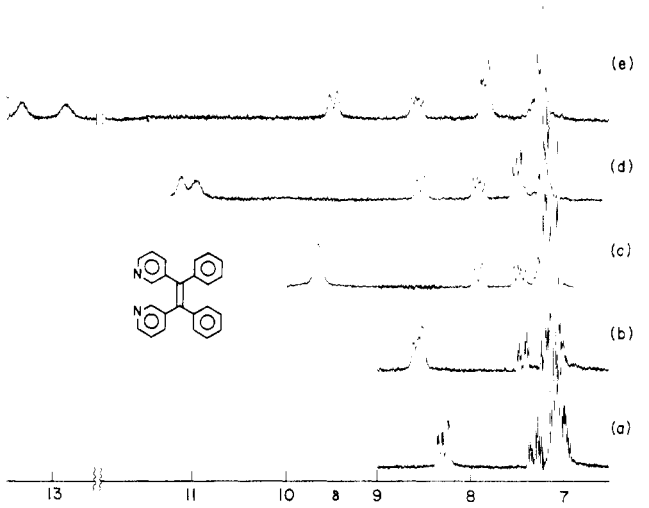
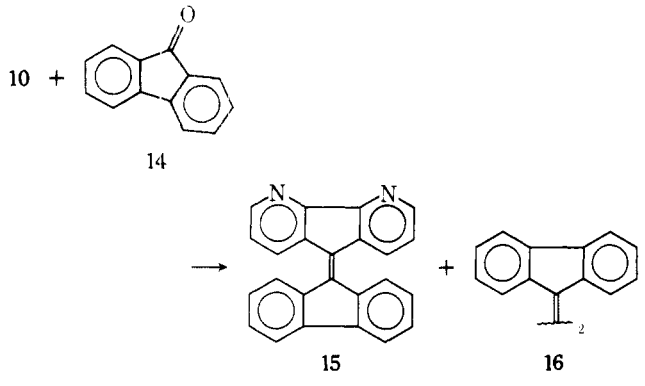


Figure 2. ^{1}H NMR (100 MHz) spectra of (*Z*)-**5** at 30 °C in $CDCl_3$ solution containing the substrate (0.16 M) at various mole ratios of Eu(fod)$_3$: (a) 0%; (b) 1%; (c) 5%; (d) 11%; (e) 21%.

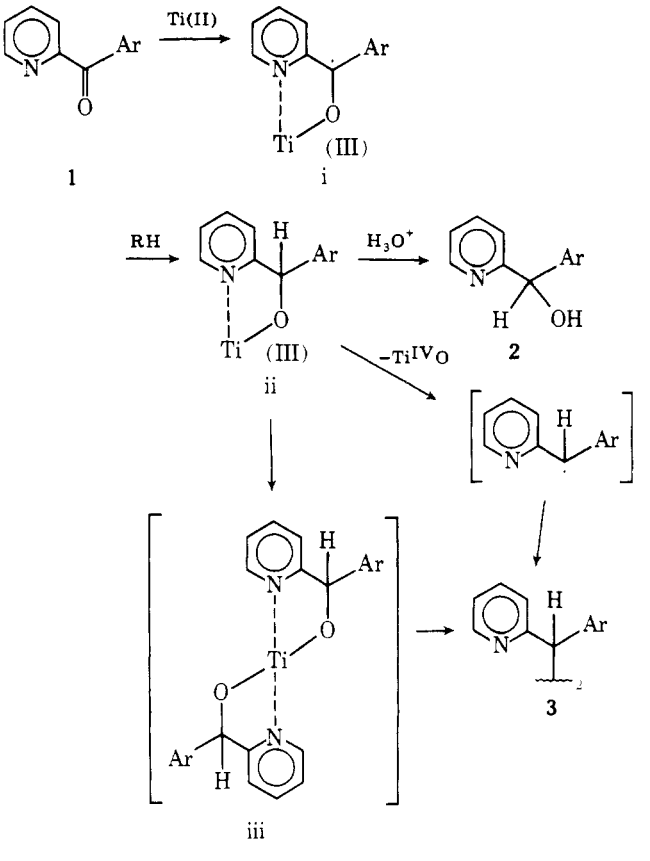
ately prior to use. Reduction of **10** with sodium borohydride gave alcohol **12** as a material highly insoluble in most organic solvents. Reductive coupling of **10** via method a afforded **13** in low yield (20%) and unchanged starting material (70+%). The structure of the high-melting ethene **13** was established in part by the distinctive upfield chemical shift of the 1,8-hydrogens (δ 7.27). That **13** exists as a dihydrate is demonstrated by the broad exchangeable singlet at δ 4.80 in the NMR spectrum and further confirmed by mass spectral data. Attempted thermal dehydration of **13** carried extensive structural decomposition.

Unsymmetrical coupling of **10** and fluorenone (**14**) was undertaken to prepare olefin **15**, by trapping of the dianion of **10** with a ketonic acceptor via an Aldol-type condensation.[3d] It has been demonstrated that the stability of the dianion of **10** is ca. 10^5 (times) greater than that of **14**.[9] Reaction of **10** with **14** under method a conditions afforded the mono hydrate of **15** in low (4%) yield; whereas, bis(fluorenylidene) (**16**) was isolated as the major product along with unchanged **10**.



The general failure of **1** (or **6**) to give the reductive coupled products can be rationalized by the initial formation of a stable intramolecular complex i, that can easily abstract a hydrogen from solvent to give ii (Scheme I). Hydrolysis of intermediate ii gives **2**, whereas reaction of ii with Ti(II) can generate a stable radical, that dimerizes to give **3**. Alternatively, the strong tendency of titantium to form TiO_2 suggests a possible complex iii, which can easily decompose to generate **3** and TiO_2. In the case of **1b** and **6**, where two sites of potential complexation are available, alternative reaction pathways are suggested, for example, by the generation of ill-defined polymeric materials. When intramolecular complexation is prevented, as with **4** and **10**, the desired reductive coupling occurs via previously considered routes;[1] lower yields of coupled products may be the result of the very limited solubility of these heteroaryl ketones.

Scheme I



Experimental Section

General Comments. All melting points were taken in capillary tubes with a Thomas-Hoover Uni-melt and are uncorrected. Infrared (IR) and ultraviolet (UV) spectra were recorded on a Perkin-Elmer 621 and Cary 14 spectrophotometers, respectively. Unless otherwise noted, ^{1}H NMR spectra were determined in deuteriochloroform (10% w/v) with Me_4Si as internal standard (δ is 0 ppm) and recorded on either a Varian Associates A-60A or HA-100 spectrometer. Mass spectral data were determined on a Hitachi Perkin-Elmer RMS-4 mass spectrometer by Mr. J. Murphy. The recorded R_f values were determined by a standardized thin-layer chromatography (TLC) procedure: 0.025-mm Brinkmann silica gel 60 HF-254 + 366 plates eluting with acetone. For preparative chromatography (ThLC), 2-mm Brinkmann silica gel PF-254 + 366 plates were used, eluting with the

stipulated solvent(s). Elemental analyses were performed by Mr. R. Seab in these laboratories.

Bis(fluorenylidene) was prepared (88%) according to the procedure of McMurry et al.,[2] [method a] from fluorenone (3.0 g, 16.6 mmol) and titanium trichloride–lithium aluminum hydride (2.5 equiv/1 equiv) in anhydrous tetrahydrofuran: mp 184–185 °C (ether–hexane) [lit.[10] mp 189–190 °C]; NMR δ 6.95–7.45 (m, 8 H), 7.55–7.80 (m, 4 H), 8.20–8.50 (m, 1,8-arom-H, 4 H).

Reaction of Phenyl 2-Pyridyl Ketone. Method a. To a slurry of $TiCl_3$–$LiAlH_4$ (2.5 equiv/1 equiv, 41.0 mmol/16.4 mmol) in THF, phenyl 2-pyridyl ketone (3.0 g, 16.4 mmol) was added. After refluxing for 12 h, the reaction mixture was cooled and then quenched with a saturated solution of aqueous potassium carbonate. The resulting suspension was filtered through a Celite pad. Both the salts and filtrate were washed and extracted with dichloromethane. The combined organic extracts were washed with water, dried over anhydrous sodium sulfate, and concentrated in vacuo to afford a yellow oil (2.8 g) which solidified on standing and was recrystallized from ether–hexane to give (93%) phenyl(2-pyridyl)methanol (**2a**): mp 72–74 °C (lit.[11] mp 78–79 °C); NMR δ 5.43 [s, –OH (exchanged with D_2O), 1 H], 5.73 (s, CHOH, 1 H), 6.90–7.65 (m, 8 H), 8.42 (ddd, 6-pyr-H, J = 5.0, 2.0, 1.0 Hz, 1 H).

Repetition of this procedure, except using 2.0 g (11 mmol) of phenyl 2-pyridyl ketone, afforded, along with phenyl(2-pyridyl)methanol (mp 72–74 °C) and unchanged starting material, 1,2-diphenyl-1,2-di(2′-pyridyl)ethane (**3a**), as a crystalline solid: mp 237–239 °C (lit.[12] mp 244–245 °C); 110 mg (6%); NMR δ 5.31 (s, benzyl-H, 2 H), 6.75–7.63 (m, pyr- and ph-H, 8 H), 8.45 (ddd, 6-pyr-H, J = 4.5, 2.0, 1.5 Hz, 2 H); MS m/e (70 eV) 336 (M^+, 28), 258 ($M^+ - C_6H_4N$, 21), 246 ($M^+ - C_7H_6$, 72), 168 ($M^+/2$, $C_{12}H_{10}N$, 100), 139 (33%). Anal. Calcd for $C_{24}H_{20}N_2$: C, H, N.

Reaction of Bis(2-pyridyl) Ketone. Method a. To a slurry of $TiCl_3$–$LiAlH_4$ (2.5 equiv/1 equiv) in THF, bis(2-pyridyl) ketone (2.0 g, 10.9 mmol) was added. After workup, a pale yellow oil (1.45 g) was isolated and chromatographed (ThLC) eluting with acetone to give the following fractions along with unchanged starting ketone.

Fraction A afforded (34%) bis(2-pyridyl)methanol (**2b**) as a colorless oil: bp 138–140 °C (1.4 mm) [lit.[13] bp 110–112 °C (1 mm)]; NMR δ 5.95 [s, CHOH (partially exchanged with D_2O), 2 H], 6.80–7.25 (m, 5-pyr-H, 2 H), 7.40–7.65 (m, 3,4-pyr-H, 4 H), 8.45 (ddd, 6-pyr-H, J = 4.5, 1.5, 0.9 Hz, 2 H); IR (neat) 3250 (br, OH), 1575, 1425 cm^{-1}.

Fraction B afforded (<1%) a beige solid: mp 112–117 °C; NMR δ 4.35 (s, CH, 2 H), 6.95–7.73 (m, pyr-H, 8 H), 8.55 (ddd, 6-pyr-H, J = 4.0, 2.0, 1.0 Hz, 2 H); MS m/e (70 eV) 370 (6), 335 (4), 343 (4), 262 (32), 184 (46), 170 (63), 157 (73), 78 (100).

Method B. Sodium (2.4 g, 4.8 equiv) was added to a slurry of $TiCl_3$ (3.35 g, 1.5 equiv) in anhydrous dimethoxyethane (DME, 65 mL) under argon. After 20 h, bis(2-pyridyl) ketone (4.0 g, 0.022 mol) in DME was added dropwise. The mixture was stirred and refluxed for 18 h, and then cooled and quenched with a saturated solution of aqueous potassium carbonate. The resultant suspension was filtered through a Celite pad. The salts were washed with dichloromethane and the combined organic material was washed with water, dried over anhydrous sodium sulfate, and concentrated in vacuo to give an orange oil, which was chromatographed (ThLC) eluting with acetone to afford starting material (45%) and bis(2-pyridyl)methanol [oil; bp 140–142 °C (2 mm); 50%].

Reaction of 3-Benzoylpyridine. To a slurry of $TiCl_3$–$LiAlH_4$ (2.5 equiv/1 equiv) in THF, 3-benzoylpyridine (2.0 g, 11.0 mmol) was added according to method a. After workup, a yellowish solid (1.78 g) was isolated and chromatographed (ThLC) eluting with ethyl acetate to give unreacted starting material and the following fractions:

Fraction A afforded the E isomer of 1,2-diphenyl-1,2-bis(3′-pyridyl)ethene, as a colorless crystalline solid from ether–acetone: mp 202–203 °C; 240 mg (13%); NMR, Figure 1; IR (KBr) 1563, 1492, 1414, 1030 cm^{-1}; MS m/e (70 eV) 334 (M^+, 100), 256 ($M^+ - C_5H_4N$, 61), 166 ($C_{12}H_8N$, 34), 148 (31), 129 (44). Anal. Calcd for $C_{24}H_{18}N_2$: C, H, N.

Fraction B gave the Z isomer of 1,2-diphenyl-1,2-bis(3′-pyridyl)-ethene, as a near colorless solid: mp 199–200 °C; 340 mg (18%); NMR, Figure 2; IR (KBr) 1563, 1492, 1414, 1030 cm^{-1}; MS m/e (70 eV) 334 (M^+, 100), 256 ($M^+ - C_5H_4N$, 86), 166 ($C_{12}H_8N$, 76), 148 (44), 129 (25). Anal. Calcd for $C_{24}H_{18}N_2$: C, H, N.

Reaction of 1,8-Diazafluorenone. To a slurry of $TiCl_3$–$LiAlH_4$ (2.5 equiv/1 equiv) in anhydrous THF, 1,8-diazafluorenone (420 mg, 2.3 mmol), prepared from 4,7-phenanthroline-5,6-quinone[4] by the procedure of Dreuy and Schmidt,[5a] was added. After stirring overnight, the reaction was quenched with saturated aqueous potassium carbonate (15 mL). The resultant brown precipitate was removed by filtration. The filtrate and residue were washed extensively with chloroform. The combined washings and extracts were washed with water, dried with anhydrous sodium sulfate, and concentrated in vacuo to afford 320 mg of a gray solid, which was chromatographed (ThLC) eluting with ethyl acetate to give two major fractions and a black solid (ca. 80%) whose structure was not determined.

Fraction A gave (12%) a yellow solid, 1,8-diazafluorenone, mp 212–215 °C.

Fraction B afforded (<1%) an off-white microcrystal: mp 143 °C dec; IR (KBr) 3490, 1575, 1415, 1100, 1025, 795 cm^{-1}; MS m/e (70 eV) 179 (6), 178 (67), 177 (100), 148 (61), 121 (53).

Reaction of 4,5-Diazafluorenone. Calcium hydride was added to a solution of 4,5-diazafluorenone (1 g, 5.55 mmol; mp 211 °C), prepared by the procedure of Eckhard and Summers,[6] in anhydrous THF (250 mL), then the stirred mixture was heated to 50 °C. This yellow solution was filtered then added dropwise to a slurry of $TiCl_3$–$LiAlH_4$ (2.5 equiv/1 equiv) as in method a. After workup, two main fractions were separated from a column chromatograph (silica gel, 60–200 mesh; Baker) and eluting with ethyl acetate afforded unreacted ketone (70+%) and bis(4,5-diazafluorenylidene) dihydrate, **13**, as colorless plates from ethanol: mp 230 °C dec; 180 mg (20%); R_f 0.17; NMR δ 4.80 [s, water of hydration (exchanged with D_2O), ca. 4 H], 6.95–7.40 (m, 1,2,7,8-arom-H, 8 H), 8.55–8.75 (dd, 3,6-arom-H, J = 5.0, 2.0 Hz, 4 H); IR (KBr) 3490 (bs, H_2O), 1620, 1395 cm^{-1}; UV (EtOH) λ_{max} 291 (ϵ 2.8 × 10^5); MS m/e (70 eV) 336 ($C_{22}H_{16}N_4$, 81) 184 (25), 170 (98), 169 (100), 142 (35). Anal. Calcd for $C_{22}H_{12}N_4 \cdot 2H_2O$: C, H, O.

Reaction of 4,5-Diazafluorenone and Fluorenone. To a slurry of $TiCl_3$–$LiAlH_4$ (2.5 equiv/1 equiv) in THF, a mixture of fluorenone (1.0 g, 5.55 mmol) and 4,5-diazafluorenone (1.0 g, 5.55 mmol) was added. After workup, a reddish-brown solid (1.28 g) was initially isolated and then chromatographed (silica gel, 60–200 mesh; Baker) eluting with ethyl acetate to give the following fractions:

Fraction A was a mixture of bis(fluorenylidene) and 9-fluorenone. Rechromatography (ThLC) of this mixture, eluting with ethyl acetate–cyclohexane (1:1), gave the red crystalline bis(fluorenylidene) [mp 182–184 °C; 14%][2a] and 9-fluorenone [mp 79 °C; 25%].

Fraction B was subsequently rechromatographed (ThLC) eluting once with ethyl acetate to afford the microcrystalline **15** as a monohydrate: mp 279–282 °C dec; 70 mg (4%); NMR δ 4.83 [s, water of hydration (exchanged with D_2O), 2 H], 6.95 (m, pyr-, arom-H, 10 H), 7.55–7.80 (m, 4 H), 8.60–8.80 (bd, 3,6-heteroaryl H, J = 4.5 Hz, 2 H); MS m/e (70 eV) 332 (95), 180 (56), 165 (100), 163 (79), 168 (95), 140 (47). Anal. Calcd for $C_{24}H_{14}N_2 \cdot H_2O$: C, H, N.

4,5-Diazafluoren-9-ol. To a suspension of 4,5-diazafluoren-9-one (100 mg, 0.54 mmol) in 95% ethanol, sodium borohydride (20 mg, 0.54 mmol) was added. The mixture was stirred for 10 min, warmed for 30 min, cooled, and diluted with water. After filtration, the filtrate was extracted with chloroform (3 × 15 mL), then the combined extracts were dried over anyydrous sodium sulfate and concentrated in vacuo to give an off-white solid (74 mg). Recrystallization from absolute ethanol gave 4,5-diazafluoren-9-ol, as a colorless solid: mp 205–207 °C (lit.[5b] mp 224 °C); 24 mg (24%). Anal. Calcd for $C_{11}H_8N_2O$: C, H, N.

1,8-Diazafluoren-9-ol was prepared in a similar manner by sodium borohydride reduction of **6**. Recrystallization from absolute ethanol gave **8** as silver needles: mp 168 °C dec; 43 mg (20%); IR (KBr) 3225 (br, OH), 1635, 1563, 1410, 1055 cm^{-1}. Anal. Calcd for $C_{11}H_8N_2O$: C, H, N.

Acknowledgments. The authors gratefully acknowledge partial support of this work by the National Science Foundation.

Registry No.—**1a,** 91-02-1; **1b,** 19437-26-4; **2a,** 14159-57-0; **2b,** 35047-29-1; **3a,** 28830-48-0; **4,** 5424-19-1; (*E*)-**5,** 68568-13-8; (*Z*)-**5,** 68568-14-9; **6,** 54078-29-4; **7,** 84-12-8; **8,** 68582-94-5; **10,** 50890-67-0; **11,** 66-71-7; **12,** 54258-37-6; **13,** 68568-15-0; **14,** 486-25-9; **15,** 68568-16-1; **16,** 746-47-4; $TiCl_3$, 7705-07-9; $LiAlH_4$, 16853-85-3.

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(6) It has been previously shown by others[7] that upon warming related diaza olefins noncharacterizable black materials are generated. Also upon treatment of either **6** or **7** with hydride ion (NaH, xylene, reflux) rapid degradation occurs to give a similar black, high-melting solid (H. C. R. Taylor, unpublished results).
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Pyrazolo[4,3-*d*]pyrimidines. Regioselectivity of N-Alkylation. Formation, Rearrangement, and Aldehyde Coupling Reactions of 3-Lithio Derivatives

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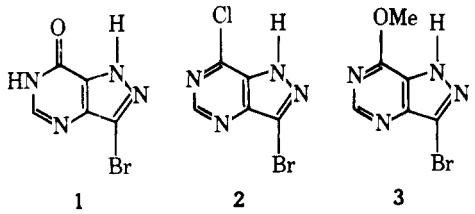
N-Alkylation reactions of 3-bromopyrazolo[4,3-*d*]pyrimidin-7-one and 3-bromo-7-chloro- and 3-bromo-7-methoxypyrazolo[4,3-*d*]pyrimidines were studied. Alkylations in aqueous base yielded predominately N-1 alkyl products, as did trimethysilylation using hexamethyldisilazane. In contrast, alkylation with 2-chlorotetrahydropyran and sodium hydride in dimethylformamide or with dihydropyran and an acid catalyst in ethyl acetate yielded predominantly N-2 alkyl products. Formation of 3-lithio derivatives of N-1 and N-2 alkylated 7-alkoxypyrazolo[4,3-*d*]pyrimidines from the corresponding 3-bromo compounds was accomplished by treatment with *n*-butyllithium at low temperatures. N-1 alkyl compounds yield complex mixtures of products, including those of N-dealkylation and rearrangement with rupture of the pyrazole ring. The N-2 alkylated compound, 3-lithio-7-methoxy-2-tetrahydropyran-2′-ylpyrazolo[4,3-*d*]pyrimidine, was stable and reacted with benzaldehyde in high yield.

In connection with research in our laboratory directed toward the development of methods for *C*-nucleoside syntheses[1] via coupling of metallo heterocyclic compounds with appropriately derivatized sugars,[2] we have investigated the utility of derivatives of 3-bromopyrazolo[4,3-*d*]pyrimidin-7-one[3] (**1**) as precursors to the corresponding 3-lithio species. Such heterocyclic organometallic compounds might serve as convenient intermediates for synthesis of the potent antibiotic formycin[1,4] and related compounds. An important aspect of the present work was a detailed study of the regioselectivity of N-alkylation of 3-bromopyrazolo[4,3-*d*]pyrimidin-7-one[3] (**1**), 3-bromo-7-chloropyrazolo[4,3-*d*]pyrimidine (**2**), and 3-bromo-7-methoxypyrazolo[4,3-*d*]pyrimidine (**3**).



1 **2** **3**

Regioselectivity of N-Alkylation. The factors which influence N-1 vs. N-2 alkylation of pyrazoles, while carefully studied,[5] are not clear. Similar studies of indazoles[6] have led to the following general rules: (1) in alkaline solutions both isomers result, generally in about equal amounts, and (2) heating with alkyl halides under neutral conditions results in exclusive or predominate N-2 substitution. Several exceptions to the first rule have been found as isopropyl, allyl, and benzyl bromides yield only the N-1 derivatives. Alkylation reactions of pyrazolo[4,3-*d*]pyrimidines are practically unknown. The reaction of formycin[1,4] with methyl iodide in ethanol containing sodium ethoxide led to isolated yields of 24% 2-methylformycin and 4% 1-methylformycin.[7]

Synthesis and Alkylation Reactions. 3-Bromopyrazolo[4,3-*d*]pyrimidin-7-one[3] (**1**) was synthesized, with modifications which led to substantial improvements in overall yield,[8] by the nine-step procedure of Robins et al.[9] The conversion of **1** to 3-bromo-7-methoxypyrazolo[4,3-*d*]pyrimidine (**3**) was effected in two steps by chlorination (phosphorus oxychloride) to yield 3-bromo-7-chloropyrazolo[4,3-*d*]pyrimidine (**2**), followed by treatment of **2** with sodium methoxide.

In Scheme I are shown the studied alkylation reactions of **1**, **2**, and **3** and interconversions which aided in proof of structures. The regioselectivities of the various alkylation reactions are listed in Table I. To obtain the data in Table I, crude product mixtures were analyzed by ^{1}H nuclear magnetic resonance (^{1}H NMR) since crystallization often led to isolation of a single product. Following the determination of N-1/N-2 alkyl isomer ratios by analysis of their ^{1}H NMR spectra, definitive structure assignments of the N-1 and N-2 alkyl isomers were made relying primarily on analysis of ^{13}C nuclear magnetic resonance spectra (^{13}C NMR). These data indicate that while N-1 alkylation is predominate in general, use of the highly reactive 2-chlorotetrahydropyran (or dihydropyran with acid catalysis) yields predominately N-2 alkylation.

Structure Assignments for N-1 and N-2 Alkylated Derivatives. Recently, Pugmire and Grant[10] and others[5b-e] have shown that ^{13}C NMR spectroscopy can be used effectively to distinguish between sites of alkylation of nitrogen heterocycles. The basic principle guiding interpretation of the ^{13}C NMR spectra of isomeric N-alkyl heterocycles is that a carbon adjacent (α) to an alkylated or protonated (i.e., trisubstituted) nitrogen resonates upfield of the signal of that same carbon in other isomers. For an N-1 alkylated pyrazolo[4,3-*d*]pyrimidine, therefore, the ^{13}C NMR absorption of C-7a will be upfield and that of C-3 will be downfield of the corresponding signals in the spectrum of the N-2 alkylated isomer.

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