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Aryne Chemistry. Part XIX.¹ Some Reactions of Tetrachloro-4-methoxypyridine with Grignard Reagents and Organolithium Compounds

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Sterically non-demanding Grignard and organolithium reagents displace the methoxy-group in tetrachloro-4methoxy-pyridine, with the formation of 4-alkyl- or 4-aryl-tetrachloropyridines. t-Butyl-lithium forms trichloro-4methoxy-3-pyridyl-lithium, which decomposes in the presence of furan with the formation of 2,3-dichloro-5,8dihydro-4-methoxy-5,8-epoxyquinoline.

PENTACHLOROPYRIDINE and pentafluoropyridine are known to undergo substitution with particular ease at the 4-position.² We have shown previously³ that pentachloropyridine reacts with n-butyl-lithium in ether to give predominantly tetrachloro-4-lithiopyridine. This compound, although considerably more stable than, for example, pentachlorophenyl-lithium,⁴ can be made to form trichloro-3-pyridyne, from which the anticipated cycloadducts with arenes were isolated in modest yield.³ Chlorinated bipyridyls were obtained as by-products in these reactions.

¹ Part XVIII, R. Harrison, H. Heaney, J. M. Jablonski, K. G. Mason, and J. M. Sketchley, J. Chem. Soc. (C), 1969, 1684. ² W. T. Flowers, R. N. Haszeldine, and S. A. Majid, Tetrahedron Letters, 1967, 2503; S. M. Roberts and H. Suschitzky, Chem. Comm., 1967, 893; R. D. Chambers, J. Hutchinson, and W. K. R. Musgrave, J. Chem. Soc., 1964, 3736; R. E. Banks, J. E. Burgess, W. M. Cheng, and R. N. Haszeldine, *ibid.*, 1965, 575. Although 3-pyridynes are well documented,⁵ 2pyridynes have not been studied in as much detail. MO calculations ⁶ suggested that 2-pyridynes should be stabilised, as compared with 3-pyridynes, by overlap of the sp^2 -hybridised lone-pair electrons on nitrogen with the sp^2 orbitals involved in forming the 'aryne' bond. Prior to the commencement of the present work only one example of a reaction involving a 2-pyridyne had been reported; ⁷ however other papers have appeared

³ J. D. Cook, B. J. Wakefield, H. Heaney, and J. M. Jablonski, J. Chem. Soc. (C), 1968, 2727.

⁴ H. Heaney and J. M. Jablonski, J. Chem. Soc. (C), 1968, 1895.

⁵ Th. Kauffmann, Angew. Chem. Internat. Edn., 1965, **4**, 543; H. J. den Hertog and H. C. van der Plas, Adv. Heterocyclic Chem., 1965, **4**, 121.

⁶ H. L. Jones and D. L. Beveridge, *Tetrahedron Letters*, 1964, 1577.

⁷ R. J. Martens and H. J. den Hertog, Tetrahedron Letters, 1962, 643; Rec. Trav. chim., 1964, 83, 621.

recently ⁸ which along with the present work establish the intermediacy of 2-pyridynes.

We argued that a suitable substituent at the 4-position in a tetrachloropyridine might not only preclude the possibility of forming a 3-pyridyne and reduce the amount of nucleophilic substitution, but also help in the



formation of a 3-lithiopyridine, which, because of the absence of chlorine at position 4, would be destabilised with respect to tetrachloro-4-pyridyl-lithium. We chose to study reactions of tetrachloro-4-methoxypyridine⁹ (1), which we were able to prepare from pentachloropyridine in 80% yield by reaction in methanol with potassium hydroxide (1 equiv.) at 0°. Unless care was taken to control the reaction conditions trichloro-2,4dimethoxypyridine⁹ (2) was also produced.

Reactions of tetrachloro-4-methoxypyridine with Grignard and organolithium reagents present interesting possibilities, The presence of an *ortho*-methoxy-group facilitates halogen-metal replacement with organolithium compounds.¹⁰ On the other hand, although the displacement of methoxy-groups by Grignard reagents is not common, it has been observed.¹¹ Replacement of the methoxy-group by an alkyl or an aryl group by reaction with a Grignard or organolithium reagent was thus conceivable, particularly in view of the presence of the electron-withdrawing chlorine atoms in tetrachloro-4-methoxypyridine. Both of these reactions have now been found to occur.

Methyl-lithium and other sterically non-demanding organolithium compounds react rapidly with tetrachloro-4-methoxypyridine at or below room temperature with the replacement of the methoxy-group and the formation of the 4-substituted tetrachloropyridine derivatives (3) in good yield.* Trichloro-2,4-dimethoxypyridine (2) reacts with methyl-lithium (1 equiv.) to form (presumably) trichloro-2-methoxy-4-methylpyridine (4) in 80% yield. These reactions were followed qualitatively by gas

* This reaction has also been observed by J. D. Cook and B. J. Wakefield (personal communication).

chromatography and were found to be essentially complete in 30 min. at 0°. Similar sterically non-demanding Grignard reagents also undergo the same reaction, but more slowly, and the reaction was only quantitative (gas chromatography) if the mixture was heated under reflux for about 2 hr. Compound (1) was, however, completely unchanged after being heated under reflux for a prolonged period with an excess of t-butylmagnesium chloride.

We were therefore encouraged to treat tetrachloro-4methoxypyridine with t-butyl-lithium. Again a rapid reaction occurred at -60° ; this was followed by hydrolysis of portions followed by t.l.c. analysis. The reaction was complete after 0.5 hr. and the remaining solution gave 2,3,6-trichloro-4-methoxypyridine (5a) in ca. 30%yield after hydrolysis. The hydrolysis product was identified from the chemical shift of the aromatic hydrogen in the n.m.r. spectrum (Table). When an excess of furan was added to a solution of the organolithium compound, and the mixture was allowed to warm to ambient temperature, we isolated 2,3-dichloro-5,8dihydro-4-methoxy-5,8-epoxyquinoline (6) in 35% yield. The structure (6) of the adduct of 5,6-dichloro-4methoxypyridyne with furan was proved by analysis and by spectroscopic and chemical methods. The dihydroderivative (7) was recovered unchanged after being

¹H N.m.r. spectra (CDCl₃ solution; 60 MHz)

Compound	-	Assignment
Compound	τ	Assignment
(1)	5.94(s)	OMe
(2)	5 ·97 (s)	OMe
	5 ·99(s)	OMe
(3a)	7·38(s)	Me
(3b)	6.92(q), 8.72(t)	$CH_2 \cdot CH_3$
(3c)	7.04(t), $8.5(m)$, $9.04(t)$	CH ₂ ·CH ₂ ·CH ₂ ·CH ₃
(3d)	2.35 - 2.85(m)	Ph
(4)	5•98(s)	OMe
	7.49(s)	Me
(5a)	3.14(s)	Aryl H
	6.01(s)	OMe
(5b)	2.8(s)	Arvl H
()	7.55(s)	Me
(5c)	2.87(s)	Arvl H
(/	$7 \cdot 2(a)$, $8 \cdot 71(t)$	CH. CH.
(6)	2.88(m)	CH=CH°
(•)	3.76(m)	CH
	4.48(m)	CH
	5.94(s)	OMe
(7)	4.14(m)	CH
(•)	4.72(m)	CH
	5.88(s)	OMe
	7.6 8.65(m)	CH CH
	(10-0-0-00(m))	U112 U112

heated with methanolic hydrogen chloride, but a quinoline derivative was obtained after a brief treatment with acetic acid containing a few drops of constant-boiling hydrogen bromide. The product had the spectroscopic properties expected for 2,3-dichloro-4-hydroxyquinoline but reproducible analytical values could not be obtained; however the mass spectrum shows ions at m/e 217, 215, and 213 in the expected ratio for a compound containing

⁸ J. D. Cook and B. J. Wakefield, *Chem. Comm.*, 1968, 297; H. N. M. van der Lans and H. J. den Hertog, *Rec. Trav. chim.*, 1968, **87**, 549.

⁹ A. Roedig, K. Grohe, and D. Klatt, *Chem. Ber.*, 1966, **99**, 2818.

¹⁰ H. Gilman, W. Langham, and F. W. Moore, *J. Amer. Chem.* Soc., 1940, **62**, 2327; see also R. G. Jones and H. Gilman, Org. Reactions, 1951, **8**, 339.

¹¹ R. C. Fuson and R. Gaertner, J. Org. Chem., 1948, 13, 496.

two chlorine atoms; therefore cleavage of the methoxygroup had occurred in addition to the aromatisation of the 1,4-epoxy-tetrahydroaromatic ring. Dechlorination of 2,3-dichloro-4-hydroxyquinoline with hydrazine hydrate in the presence of palladium-carbon¹² gave material in low yield which had a spectrum identical with that quoted ¹³ for 4-hydroxyquinoline, and showed no mixed m.p. depression ¹⁴ with an authentic sample.

Tetrachloro-4-methylpyridine is not a suitable compound from which to prepare pyridyl-lithium reagents. The reaction of n-butyl-lithium with tetrachloro-4methylpyridine gave a deep red solution which after hydrolysis was shown by n.m.r. spectroscopy to consist of unchanged starting material contaminated with material (20%) having the ¹H n.m.r. spectrum expected for 2,3,6-trichloro-4-methylpyridine. Carboxylation of the above solution or organolithium reagents gave a mixture of acids which were esterified with diazomethane. Gas chromatography showed the presence of two esters in the ratio 4:1. Separation of these compounds by chromatography gave methyl 2,3,5,6-tetrachloro-4-pyridylacetate (the major product) and methyl trichloro-4methylnicotinate.

EXPERIMENTAL

For general directions see Part XVIII.¹

Tetrachloro-4-methoxypyridine.—A solution of pentachloropyridine (50 g.) in methanol (4 l.) was cooled to 0° prior to the addition of potassium hydroxide (12 g., 1 mole). The solution was stirred at 0° for ca. 5 hr., then allowed to warm slowly to room temperature. After a total of 15 hr. hydrochloric acid (25 ml.) was added and a small amount of suspended material was filtered off. The filtrate was evaporated (below 50°) and the residue was washed with water until free from chloride ions. The dried product gave tetrachloro-4-methoxypyridine (40 g., 81%), m.p. 113.5° (from methanol) (lit.,⁹ 117—119°) (Found: C, 29.4; H, 1.3; N, 5.75. Calc. for C₆H₃Cl₄NO: C, 29.2; H, 1.2; N, 5.65%).

In a similar reaction, but without the temperature control we obtained trichloro-2,4-dimethoxypyridine (85%), m.p. 116·5—117·5 (lit.,⁹ 124—125°) (Found: C, 34·9; H, 2·7; N, 5·75. Calc. for $C_7H_6Cl_3NO_2$: C, 34·65; H, 2·5; N, 5·8%).

Tetrachloro-4-ethylpyridine.—A solution of tetrachloro-4methoxypyridine (5 g., 0.02 mole) in ether (50 ml.) was added rapidly, with stirring, to a solution of ethylmagnesium bromide in ether [from bromoethane (3.3 g., 0.03 mole)]. A white precipitate gradually formed and after 1 hr. a sample of the mixture was removed, hydrolysed, and analysed by t.l.c. A small amount of starting material was still present. The mixture was then heated under reflux for 0.5 hr., after which time no starting material remained. Conventional work-up gave tetrachloro-4-ethylpyridine (4 g., 80%), m.p. and mixed m.p. $67.5-68.5^{\circ}$ * (lit., ¹⁵ 74-75°) (Found: C, 34.3; H, 2.0; N, 5.65. Calc. for C₇H₅Cl₄N: C, 34.3; H, 2.05; N, 5.7%).

A similar reaction with n-butylmagnesium bromide gave 4-n-butyltetrachloropyridine (75.5%), b.p. 140-145°/3 mm.

(Found: C, 40·15; H, 3·7; N, 5·15. C₉H₉Cl₄N requires C, 39·6; H, 3·3; N, 5·15%).

Tetrachloro-4-methylpyridine.—A solution of methyllithium [from bromomethane (15 g.)] was added during 1 hr. to a solution of tetrachloro-4-methoxypyridine (24.6 g., 0.1 mole) in ether (400 ml.) at 10°. The resulting solution was stirred at room temperature for a further 2 hr. and water (100 ml.) was added. The product gave tetrachloro-4-methylpyridine (22.4 g., 97%), m.p. 88.5—86.5 (from methanol) (Found: C, 31.45; H, 1.45; N, 6.0. C₆H₃Cl₄N requires C, 31.15; H, 1.3; N, 6.05%).

Cognate reactions gave trichloro-2-methoxy-4-methylpyridine (78%), m.p. 82° (from ether) (Found: C, 36.7; H, 2.8; Cl, 46.65. $C_7H_6Cl_3NO$ requires C, 37.1; H, 2.65; Cl, 47.0%), and tetrachloro-4-phenylpyridine (80%), m.p. 137— 138° (from ethanol) (Found: C, 45.0; H, 2.0; N, 4.6. $C_{11}H_5Cl_4N$ requires C, 45.05; H, 1.7; N, 4.8%).

Reaction of Tetrachloro-4-methoxypyridine with t-Butyllithium.—A solution of t-butyl-lithium in hexane was added during 0.5 hr. to a solution of tetrachloro-4-methoxypyridine (5 g., 0.02 mole) in ether at -60° . The mixture was maintained at -60° for a further 2 hr., after which time hydrolysis of a portion and analysis by t.l.c. showed no starting material to be present. The mixture was added to ice and after work-up a crystalline solid (2·1 g.) was obtained. Recrystallisation from light petroleum and then ethanol gave 2,3,6-trichloro-4-methoxypyridine (1·1 g., 26%), m.p. 136·5—137·5° (Found: C, 33·8; H, 2·2; N, 6·7. C₆H₄Cl₃-NO requires C, 33·9; H, 1·9; N, 6·6%).

Reaction of Tetrachloro-4-methylpyridine with n-Butyllithium.—A solution of n-butyl-lithium (1 equiv.) was added to tetrachloro-4-methylpyridine (3.45 g.) in ether (100 ml.) at -60° during 15 min. After 1 hr. at -60° hydrolysis of a portion and examination by gas chromatography showed that the mixture contained starting material (ca. 80%). Dry carbon dioxide was then passed through the mixture at -60° for 3 hr. Conventional work-up gave a light brown crystalline acidic product (3.4 g.), which was methylated with diazomethane and gave a mixture of esters (3.4 g.) containing two components in the ratio of 4:1 (gas chromatography). The major product was isolated by crystallisation from ethanol and gave methyl tetrachloro-4pyridylacetate, m.p. 84.5-85°, 7 5.96 (2H,s) and 6.30 (3H,s) (Found: C, 33.65; H, 1.65; N, 4.9. C₈H₅Cl₄NO₂ requires C, 33.25; H, 1.75; N, 4.85%). Evaporation of the mother liquors gave an oil which was placed on a column of neutral alumina. Elution with light petroleum containing increasing amounts of benzene gave methyltrichloro-4-methylnicotinate, b.p. ca. 180°/1.0 mm., 7 6.10 (3H,2, OMe) and 7.65 (3H,s, Me).

Reaction of Tetrachloro-4-ethylpyridine with n-Butyllithium.—A similar reaction to that just described gave, after hydrolysis of the lithium reagent, 2,3,6-trichloro-4ethylpyridine (51%), b.p. $180^{\circ}/1.5$ mm. (Found: C, 39.5; H, 3.15. C₇H₆Cl₃N requires C, 39.55; H, 2.8%).

Reaction of 5,6-Dichloro-4-methoxy-2-pyridyne with Furan. —Redistilled furan (150 ml.) was added to a solution of trichloro-4-methoxy-3-pyridyl-lithium at -60° during 0.5 hr. The mixture was allowed to warm to ambient tempera-

¹² W. L. Mosby, Chem. and Ind., 1959, 1348; J. Org. Chem., 1959, **44**, 421.

¹³ G. W. Ewing and E. A. Steck, J. Amer. Chem. Soc., 1946, **68**, 2181.

¹⁴ R. Camps, Ber., 1901, 34, 2703.

¹⁵ S. S. Dua and H. Gilman, J. Organometallic Chem., 1968, **12**, 299.

^{*} Sample, m.p. $67\cdot5-68\cdot5^{\circ}$, supplied by Professor H. Gilman. A sample prepared by another route by J. D. Cook and B. J. Wakefield (*J. Chem. Soc.* (*C*), in the press) is also identical.

ture slowly and was then set aside overnight. After the usual work-up a crystalline product (4.5 g.) was obtained and was placed on a column of neutral alumina. Elution with light petroleum and then benzene removed small amounts of tetrachloro-4-methoxypyridine and 2,3,6-trichloro-4-methoxypyridine. Finally elution with ethyl acetate gave 2,3-dichloro-5,8-dihydro-5,8-epoxy-4-methoxy-quinoline (1.7 g., 35%), m.p. 132.5° (from benzene-light petroleum) (Found: C, 49.2; H, 2.9; N, 5.7. C₁₀H₇Cl₂NO₂ requires C, 49.2; H, 2.9; N, 5.75%).

Hydrogenation of the Adduct.—Use of palladium–carbon catalyst gave 2,3-dichloro-5,6,7,8-tetrahydro-4-methoxy-5,8-epoxyquinoline (80%), m.p. 130.5—131.5° (from ethanol) (Found: C, 49.3; H, 3.75; N, 5.85. $C_{10}H_9Cl_2NO_2$ requires C, 48.8; H, 3.7; N, 5.7%).

Aromatisation of the Dihydro-adduct.—The hydrogenated adduct (210 mg.) in acetic acid (10 ml.) and hydrobromic acid (2 ml.) was heated on a steam-bath for 2 hr., and poured into water (50 ml.). Filtration gave 2,3-dichloro-4hydroxyquinoline (110 mg.), m.p. 279—280° (from ethanol), λ_{max} (MeOH) 220 (ε 16,120), 245 (16,740), 251 (17,780), 283 (1255), 295 (1925), 312.5 (3850), 322 (5357), and 334 (5273) nm., m/e 217, 215, 213, 180, 178, 152, and 150.

Dechlorination of 2,3-Dichloro-4-hydroxyquinoline.—2,3-Dichloro-4-hydroxyquinoline (25 mg.) in ethanol (10 ml.) containing palladium-carbon (10%; 20 mg.) was heated under reflux while hydrazine hydrate (0.8 ml.) was added. Heating was continued for a further 0.5 hr. and the mixture was filtered. The filtrate was evaporated under reduced pressure. The residue was dissolved in ethyl acetate, washed with aqueous sodium carbonate, dried, and evaporated. The residue thus obtained was subjected to t.1.c. on silica and eluted with acetone to give 4-hydroxyquinoline (5 mg.), having i.r. and u.v. spectra identical with those of an authentic sample, m.p. and mixed m.p. 201° (lit., ¹⁴ 201°).

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