Cu(I) Substitutions. Furo[3,2-*b*]pyridines, Furo[3,2-*c*]pyridines and 1*H*-Thieno[3,4-*b*]2-pyran-1-ones from Cuprous Acetylides

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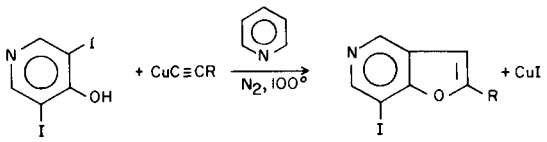
The reaction of cuprous acetylides with aryl halides bearing a nucleophilic *ortho* substituent provides a versatile route to heterocyclic substances. The present work portrays the ease with which polyheterosystems can be constructed with this reaction. The synthesis of 2-substituted 7-iodofuro[3,2-c]pyridines, 2-substituted furo[3,2-*b*]pyridines, and 3-substituted 1*H*-thieno-[3,4-*b*]-2-pyran-1-ones (thiaisocoumarins) is described. The latter two ring systems have not been previously reported.

As part of a study of the substitution of organic molecules by ligands of transition metals, we have described a general heterocyclic synthesis (equation 1). The reaction entails the substitution of a carbon-halogen bond with a cuprous acetylide and subsequent or synchronous copper catalyzed addition of the neighboring nucleophilic substituent to the triple bond. The high utility of the reaction for the synthesis of aryl acetylenes (2,3), indoles (2), benzofurans (2), phthalides (2), benzo[*b*]thiophenes (8) and furans (5) has been reported. We now wish to amplify the ease with which the reaction can be applied to other heterocyclic systems. The versatility of this synthetic path is exemplified in the present work by the facile preparation of furo[3,2-*c*]pyridines, furo[3,2-*b*]pyridines and 1*H*-thieno[3,4-*b*]-2-pyran-1-ones (thiaisocoumarins). The first of these systems has been obtained by an arduous route which proceeds through a final palladium on carbon aromatization (4) of the 6,7-dihydro derivatives (4,7). In a prelude to the present work, we have described the 2-phenyl-7-iodo derivative (2). The latter two systems have not been previously prepared.

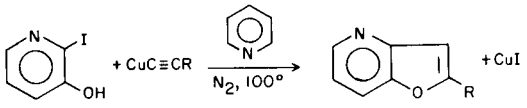
(1)

X = halogen, QH = nucleophilic group



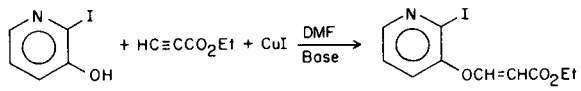
(2)

R = *n*-hexyl (37%), *n*-propyl (24%), β-hydroxyethyl (49%), phenyl (86%), and α-pyridyl (37%)



(3)

R = phenyl (84%), *n*-propyl (82%), *n*-butyl (88%), *n*-hexyl (92%), β-hydroxyethyl (61%)



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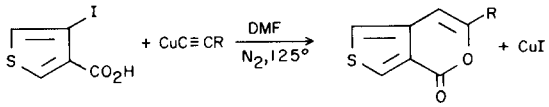
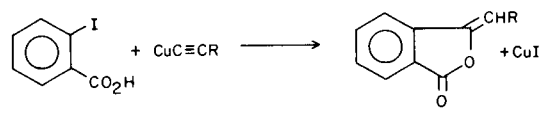


(5)

R = phenyl (57%), *n*-propyl (85%), *n*-butyl (78%), *n*-hexyl (30%)



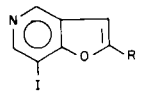
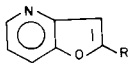
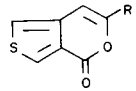
(6)

Furo[3,2-c]pyridines.

Starting with commercially available 3,5-diiodo-4-pyridinol, 2-substituted 7-iodofuro[3,2-*c*]pyridines are readily obtained according to equation 2. The yields noted are for purified product. These conversions are of heightened interest because the keto tautomer is the dominant form of the pyridinols in the solid state and in solution (6). However, the products of these transofmrations clearly contain the furan ring (10) in keeping with the conversion of α-halo ketones to furans (5) under related conditions. These results taken together suggest that Cu(I) can catalyze the enolization and that cyclization occurs through a copper coordinated enolacetylene.

TABLE I

Reaction Conditions and Product Characteristics

	R	Solvent (temp.)	Elemental Analysis, Calcd. (Found) C	H	N	b.p. or m.p. (recryst. solvent)	Spectral IR (cm^{-1}) (b)	nmr
	phenyl (a)	DMF, 120°	48.62(48.97)	2.51(2.92)	4.36(4.58)	134° (ethanol-water)	1270,1159(C-O)	
	α-pyridyl	pyr., 100°	44.78(45.00)	2.19(2.37)		183-184°(ethanol-water)	1255,1150(C-O)	1.0 δ (trip. 3H), 1.7 (sextet, 2H), 2.75 (triplet 2H), 6.6 (singlet, 1H).
	n-propyl	pyr., 70°	41.85(42.05)	3.51(3.86)	4.88(4.74)	108-109°(0.5 mm)	1270,1129(C-O)	
	n-hexyl	pyr., 100°	47.49(47.97)	4.91(5.02)	4.26(4.46)	59-60° 140-143°(0.5 mm) 36°(methanol-water)	1242,1155(C-O)	
	β-hydroxy-ethyl	pyr., 100°	37.40(37.64)	2.79(3.27)	4.85(4.69)		3160(OH)1260,1142, 1060(C-O)	
	phenyl	pyr., 100°	79.98(79.62)	4.65(4.80)	7.17(7.18)	93-95°(sublimed) (isooctane)	1248(C-O)	
	*n*-propyl picrate	pyr., 100°	49.23(49.26)	3.62(3.78)	14.36(14.48)	110-111°(8 mm) 159-160°(ethanol)	1255(C-O)	0.78 δ (triplet, 3H), 1.46(sextet 2H), 2.48 (triplet, 2H), 6.38 (singlet, 1H) multiplets at 6.88, 7.36, 8.30.
	n-butyl picrate	DMF,100°	50.50(50.63)	3.99(4.15)	7.99(8.00) 13.86(13.75)	121°(8 mm) 141-143°(ethanol)	1260(C-O)	
	n-hexyl picrate	pyr., 100°	52.78(52.73)	4.66(4.78)	6.89(6.89) 12.96(12.92)	150.5°(8 mm) 109-110°(ethanol)	1255(C-O)	
	β-hydroxy-ethyl picrate	pyr., 100°	45.92(46.18)	3.08(3.29)	8.58(8.96) 14.28(14.44)	151-152°(0.5 mm) 157-159°(ethanol	3260(OH)1260, 1245(C-O)	
	phenyl	DMF, 125°	68.40(67.87)	3.53(3.56)	S 14.04(13.71)	110-111°(ether-petroleum ether)	1730(C=O)	6.84 δ (singlet) 7.40, 7.858 (multiplet)
	n-propyl	DMF, 125°	61.90(61.87)	5.15(5.40)	16.50(17.15)	128-130°(2 mm)	1730(C=O)	0.958(triplet, 3H) 1.67(sextet, 2H) 2.32(triplet, 2H) (singlets 1H) at 6.07, 7.06, 8.23.
	n-butyl	DMF, 125°	63.45(63.37)	5.81(5.96)	15.37(15.58)	135-140°(2 mm)	1730(C=O)	
	n-hexyl	DMF, 125°	66.08(65.97)	6.83(6.97)		~135°(0.5 mm)(c)	1725(C=O)	

(a) This compound has been described (ref. 2). (b) Except for the 1240-1270 cm^{-1} band in the iodofuro[3,2-*c*]pyridines, all bands are strong. (c) The substance was purified by Kugelrohr distillation.

Furo[3,2-*b*]pyridines.

Reaction of the acetylides with 2-iodo-3-pyridinol proceeds smoothly in pyridine or dimethylformamide according to equation 3. The better yields reflect a greater stability of the non-iodinated 2-substituted furo-[3,2-*b*]pyridines. Attempts to form the 2-carbethoxy derivative via an *in situ* generation of the acetylide (2) from ethyl propiolate cuprous iodide and *N*-ethylpiperidine or 1,4-diazabicyclo[2.2.2.]octane in dimethylformamide resulted in the addition product (equation 4). The intermolecular addition is quite analogous to the copper catalyzed intramolecular cyclizations noted herein.

1*H*-Thieno[3,4-*b*]-2-pyran-1-ones.

The preparation of these materials proceeds readily from 3-iodo-4-carboxythiophene in dimethylformamide (equation 5). In contrast to *o*-halobenzoic acids, 3-iodo-4-carboxythiophene does cyclize to the six membered "thiaisocoumarin" structure. The corresponding benzoic acids yield phthalides under identical conditions (2) (equation 6). The pyranone structure of the above substances (equation 5) is affirmed by their infrared (11) and nmr spectra (*cf.* Table I). A more favorable geometry for 5-6 rather than 5-5 ring formation would be anticipated.

This work points up the ease with which cuprous acetylides may be employed to build heterocyclic moities upon other heterocyclic units and suggests an exceedingly broad scope for the reaction in polyhetero systems.

EXPERIMENTAL

Materials.

The following compounds were obtained commercially and were employed directly: 3,5-diiodo-4-pyridinol (Aldrich), 2-iodo-3-pyridinol (Aldrich). The 3-iodo-4-carboxythiophene was prepared from thiophene according to Steinkopf and Hanske (9).

Acetylides were prepared in the manner previously described (2).

Reactions.

All reactions were carried out in a nigrogen atmosphere. Typical cases are presented below.

2-*n*-Butylfuro[3,2-*b*]pyridine.

A three-necked flask equipped with a magnetic stirring bar, nitrogen inlet and a reflux condenser connected to a mercury trap was flushed with nitrogen and charged with 80 ml. of dimethylformamide. The solvent was stirred under a nitrogen sweep for 30 minutes. Under nitrogen, 2.17 g. (0.015 mole) of cuprous *n*-butylacetylide and 3.30 g. (0.015 mole) of 2-iodo-3-pyridinol were added. The stirred mixture was warmed in an oil bath to 100° and maintained at that temperature for 15 hours. A slow nitrogen stream was passed through the apparatus during the course of the reaction. After cooling, the reaction mixture was filtered, and the dimethylformamide was removed *in vacuo* with a rotary evaporator. The concentrate was treated with 50 ml. of 28% ammonium hydroxide and 100 ml. of ether. The whole was shaken vigorously. The aqueous phase was extracted twice with ether. The combined ether solutions were washed three times each with concentrated ammonium hydroxide and water, and then dried over magnesium sulfate. The solution was concentrated and the residual oil was distilled through a small Vigreaux column to yield 2.30 g. (0.0132 mole, 88%) of 2-*n*-butylfuro[3,2-*b*]pyridine as a colorless oil having b.p. 121° (8 mm). The infrared spectrum showed a strong band at 1260 cm^{-1}.

Anal. Calcd. for $C_{11}H_{13}NO$: N, 7.99. Found: N, 8.00.

A picrate was prepared and recrystallized thrice from ethanol. Bright yellow needles with m.p. 141-143° were obtained.

Anal. Calcd. for $C_{17}H_{16}N_4O_8$: C, 50.50; H, 3.99; N, 13.86. Found: C, 50.63; H, 4.15; N, 13.75.

3-*n*-Propyl-1*H*-thieno[3,4-*b*]-2-pyran-1-one.

A mixture of 1.3 g. (0.0005 mole) of 3-iodothiophene-4-carboxylic acid and 0.68 g. (0.0005 mole) of cuprous propylacetylide in 50 ml. of dimethylformamide at 125° for 16 hours afforded upon work up 1.01 g. of a yellow oil. Thin layer chromatographic analysis indicated the oil to be a mixture of two compounds. The smaller component was presumed to be 1,4-dipropylbutadiyne. The presence of trace amounts of coupling products from these preparations can be eliminated if fresh acetylide is employed and oxygen is excluded during the reaction.

The oil was chromatographed on a neutral silica gel column. The product was eluted successively with petroleum ether-ethyl acetate of increasing polarity and finally with 5% methanol in chloroform. The latter fractions were combined, concentrated and the residue distilled to yield 0.85 g. (0.043 mole, 85%) of pure 3-*n*-propyl-1*H*-thieno[3,4-*b*]2-pyran-1-one, b.p. 128-130° (2 mm); infrared spectrum: C=O at 1730 cm^{-1}; n.m.r.: 0.95 δ (triplet, 3H), 1.67 (sextet 2H), 2.32 (triplet 2H) and singlets at 6.07, 7.068 and 8.23, all 1H.

Anal. Calcd. for $C_{10}H_{10}O_2S$: C, 61.90; H, 5.15; S, 16.50. Found: C, 61.87; H, 5.40; S, 17.15.

Ethyl β-2-Iodo-3-pyridoxyacrylate.

A mixture of 6.6 g. (0.03 mole) of 2-iodo-3-pyridinol, 2.94 g. (0.03 mole) of ethyl propiolate, 5.74 g. (0.03 mole) of cuprous iodide and 3.85 g. (0.03 mole) of 1,4-diazabicyclo[2.2.2]octane in 100 ml. of dimethylformamide at 140° for 16 hours afforded, in similar fashion, 3.7 g., (0.016 mole, 39%) of product having b.p. 146-148° (0.5 mm.); infrared: 1705 cm^{-1} (C=O); nmr: 1.2 (triplet, 3H), 4.12 (quartet, 2H), 5.56 (doublet, 1H0, 7.31 (multiplet 2H), 7.64 (doublet, 1H), 8.17 (multiplet, 1H).

Anal. Calcd. for $C_{10}H_{10}INO_3$: C, 37.64; H, 3.20; N, 4.38. Found: C, 37.49; H, 3.31; N, 4.07.

Salient information for other compounds is given in Table I. With the exceptions of the first substance listed the compounds have not been reported.

Acknowledgment.

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(1) To whom inquiries should be addressed.

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(10) The infrared spectrum of these materials shows no absorption due to C=O, C≡C, NH or OH (except for the 2-hydroxyethyl derivatives). See Table I for C-O assignments.

(11) The ~ 1730 cm^{-1} C=O bond closely resembles that of the corresponding isocoumarins. The phthalide carbonyl is in the range of 1775 cm^{-1}. More importantly the vinyl proton of the isocoumarin structure is a singlet.

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