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COUPLING REACTIONS OF METHOXYBUTENYNYL COPPER - A FACILE ROUTE TO SUBSTITUTED INDOLES

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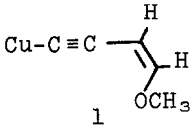
Cuprous acetylide coupling reactions with aromatic compounds afford an efficient and operationally convenient approach to the synthesis of aromatic natural products.[1] This method has been recently utilized for the synthesis of junipal.[2] In connection with research directed toward the synthesis of indole alkaloids, we report the preparation and reactions of 1, a versatile and



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hitherto unreported copper acetylide. This compound can be prepared from commercially available methoxybutenyne[3] by a modification[4] of the method of Castro[5] in 75% yield. This air-sensitive yellow solid reacts with aryl halides in hot pyridine[6] under conditions in which oxygen must be rigorously excluded. In the presence of oxygen, the symmetrical diacetylene is the major product. Results with representative halides are illustrated in Table I. Interestingly, the reactions of 1 at ambient temperature with o-bromoaniline or m-nitro-o-bromoaniline produced only tarry products. The use of adducts 3 for elaboration into 2-substituted indoles shows the synthetic potential of 1. The initial scheme involved enol ether hydrolysis, protection, reduction and subsequent cyclization. The enol ether proved to be unexpectedly resistant to mild acid hydrolysis (HCl, aq.EtOH; 20% H_2SO_4, 0°C)[7] and decomposed under more vigorous conditions. Experimental attention was then directed to addition of methanol to the acetylene. Although mercuric sulfate catalyzed addition provided a complex product mixture, potassium hydroxide in refluxing methanol (4 hr) afforded a mixture of isomeric enol ethers 4.[8]

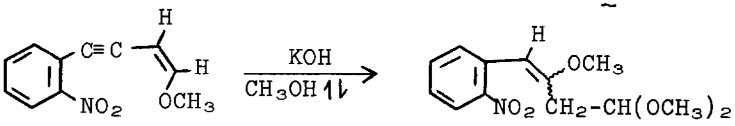

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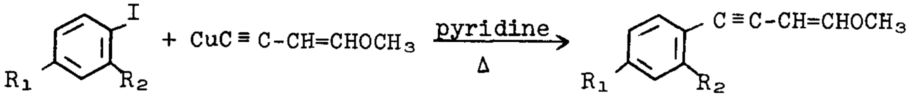
Table I - Coupling Reactions of $CuC{\equiv}C\text{-}CH{=}CHOCH_3$



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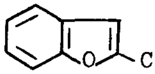
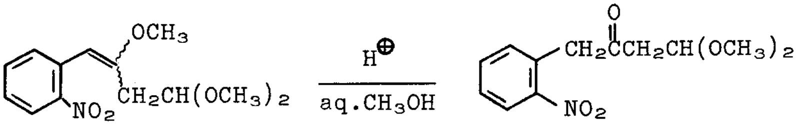
R_1	R_2	Reaction time (hr), temperature	Yield(%)[a]	NMR($CDCl_3$)
NO_2	H	10,85°	87	3.83(s,3H), 4.75(d,J=6Hz,1H), 6.40 (d,J=6Hz,1H), 7.8(d of d, 4H).
H	OH	10,125°	60[b]	(cis)3.73(s,3H), 5.54(d,J=6Hz,1H), 6.18(d,J=6Hz,1H), 7.00-7.60(m,5H). (trans)3.53(s,3H), 5.72(d,J=13Hz, 1H), 6.3(s,1H), 7.0-7.6(m,5H).
H	H	10,125°	63	3.9(s,3H), 4.80(d,J=6Hz,1H), 6.40 (d,J=6Hz,1H), 7.2-7.8(m,5H).
H	NO_2	10,85°	94	3.95(s,3H), 4.87(d,J=6Hz,1H), 6.55 (d,J=6Hz,1H), 7.3-8.2(m,4H).
CH_3O	NO_2	10,85°	93	3.70(s,3H), 3.72(s,3H), 4.65(d,J=6Hz,1H), 6.36(d,J=6Hz,1H), 6.98-7.75(m,4H).
CH_3	H	10,120°	65	90:10 cis: trans vinyl ether mixture (cis) 2.36(s,3H), 3.87(s,3H), 4.75 (d,J=6Hz,1H), 6.35(d,J=6Hz,1H), 7.25(d of d,4H), (trans) 2.36(s,3H), 3.66(s,3H), 5.13(d,J=13hz,1H), 7.03 (d,J=13Hz,1H), 7.25(d of d, 4H).
Cl	H	12,100°	79	3.85(s,3H), 4.75(d,J=6Hz,1H), 6.33 (d,J=6Hz,1H), 7.37(d of d,4H).

[a] Isolated yield, all compounds possess satisfactory IR,NMR,UV and high resolution mass spectra.

[b]  $C{\equiv}C\text{-}CH{=}CHOCH_3$, 65:35 cis:trans mixture.

This mixture could be selectively hydrolyzed in aqueous methanol at ambient temperature to yield ketoacetal 5[9] in 55% yield from 3. Transformation of 5



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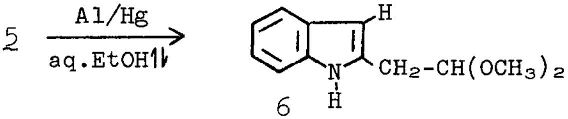
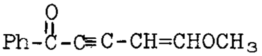
into indole-2-acetaldehyde dimethylacetal 6 was accomplished by reduction with aluminum amalgam in refluxing aqueous ethanol.[10] The only product isolated in 75% yield after alumina chromatography was indole 6. In contrast,



the reagents typically used for reduction of an aromatic nitro group (Zn,EtOH; Pd/C, cyclohexene; $SnCl_2$) gave only traces of the desired indole. The structural assignment for 6 was supported by UV(EtOH): 205, 221, 278, 282, 289; IR(film): 3395, 2930, 2835, 1110, 1060, 750 and NMR($CDCl_3$): 3.19(d,J=6Hz,2H), 3.46(s,6H), 4.64(t,J=6Hz,1H), 6.22(s,1H), 7.0-7.6(m,4H). The indole-2-acetaldehyde moiety is a key component in the structures of curare alkaloids.[11] Additionally it will serve as a convenient building block for many other indole alkaloids.

Cuprous acetylide 1 also reacts readily with benzoyl chloride[12] to form 7 (45%; 3.93(s,3H), 4.81(d,J=6Hz,1H), 6.72(d,J=6Hz,1H), 2180, 1635, 1605cm^{-1}), allyl bromide[13] to produce 8 (63%, 3.0-3.25(m,2H), 3.75(s,3H), 4.5(m,1H), 4.9-6.3(m,4H); 1640, 1270cm^{-1}), benzyl bromide to afford 9 (72%, 3.78(bs 5H), 4.60(m,1H), 6.26(d,J=6Hz,1H), 7.2-7.5(m,5H)) and trans-1-iodo-1-hexene[14] to give 10 (69%, .8-2.25(m,9H), 3.78(s,3H), 4.60(d of d, J=6, 2.5Hz,1H), 5.4-6.4 (m,3H); 1640, 1270cm^{-1}).



$Ph\text{-}\overset{O}{\overset{\|}{C}}\text{-}C{\equiv}C\text{-}CH{=}CHOCH_3$

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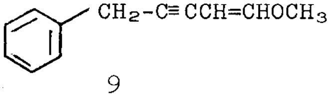
$CH_2{=}CHCH_2C{\equiv}CCH{=}CHOCH_3$

8



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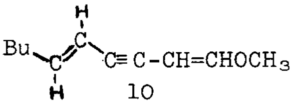

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References and Notes:

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2. R. E. Atkinson, R. F. Curtis, G. T. Phillips, Chem. Ind., 1964, 2101.
3. The commercial compound (from Aldrich) is a 50% solution in aqueous methanol. It is diluted with brine, extracted with ether, dried and distilled.
4. For optimal yields it is best to add the methoxybutenyne as a 4M solution in ethanol. Larger volumes of ethanol drastically decrease the isolated yield of cuprous acetylide.
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9. IR(film): 2930, 2830, 1715, 1520, 1340; NMR($CDCl_3$): 2.95(d,J=5Hz,2H), 3.44(s,6H), 4.23(s,2H), 4.88(t,J=5Hz,1H), 7.2-8.25(m,4H).
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