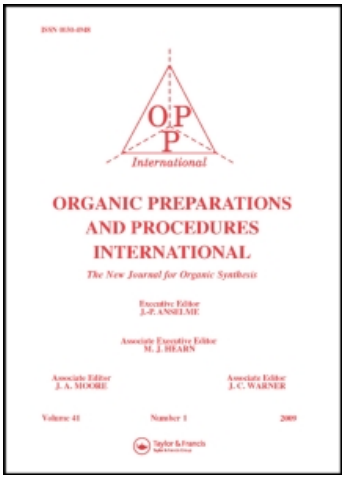

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A SIMPLE PREPARATION OF 1-ALKOXY-1-ALKYN-3-OLS

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A SIMPLE PREPARATION OF 1-ALKOXY-1-ALKYN-3-OLS

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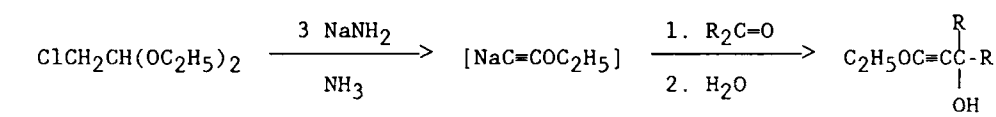
The reported methods for the synthesis of the title compounds are unnecessarily long, requiring many steps.[1,2] Recently, two alternative syntheses using butyllithium as a base have been reported.[3] Both Smithers' multistep procedure which produced 1a in a 42% yield from readily available starting materials and Raucher's method (95% yield), seem best suited for small scale reactions. The present work describes an extension of an excellent general synthesis for the production of 1-alkoxy-1-alkynes.[4] This one-pot preparation of the title compounds is the simplest high yielding method yet reported.



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a) R = CH_3 (35% yield) b) R = C_2H_5 (48% yield) c) R = i-C_3H_7 (73% yield)

Even though 1a is produced in a modest 35% yield, the reaction gives higher yields with the more substituted analogs. The coupling reaction between the ethoxyalkynide salts and ketones have been reported to proceed almost instantaneously even at -30°; however, low yields are often obtained when the carbonyl compound is relatively acidic.[5] In these cases, enolization competes with the desired addition reaction, and the

yield of 1-ethoxyalkynols decreases. Since the yields reported here directly parallel the acidity order of the ketones,[6] there is no reason to doubt that the competing enolization reaction of the ketone is a major factor in determining product yield. Because of similar problems, workers have tended to use lithium alkynides rather than the corresponding sodium salts for the synthesis of 1-alkoxyalkynols with the assumption that the more covalent lithium species are less basic and will give rise to less enolization. In the hope of increasing the yield, two trials were made under varying conditions to determine if lithium ethoxyalkynides could be made directly from chloroacetaldehyde diethyl acetal and lithium amide with subsequent addition to a ketone. The one reference that reports this reaction states that only the starting material is recovered.[7] In our study, product was also isolated. Using the standard procedure, 1a was produced in 5% yield while 83% of the starting acetal was recovered. Since solvent effects are known to be important in these reactions,[1,2] another trial in hexamethylphosphoramide resulted in an increase in product yield to 34% of 1b with a concomitant reduction of unreacted acetal to 28%. Extrapolation of this ratio to 100% conversion of acetal would give almost exactly the same yield for 1b as was obtained using the sodium amide procedure. Hence, no further studies were performed with lithium amide since the sodium alkynide salts formed more rapidly, gave approximately the same yields and did not require the use of cosolvents to force the reaction to completion.

EXPERIMENTAL SECTION

IR spectra were recorded neat on a Beckman 4240 spectrophotometer and are referenced to polystyrene. ^{1}H-NMR spectra were obtained on a JEOL FX90Q spectrometer and are reported in parts per million (δ) from the internal standard Me_4Si. GC analyses were made on a Hewlett-Packard 5791 capillary chromatograph with FID (0.25 mm X 60 m J&W Carbowax 20M column programmed to hold at 50° for 8 min with a 4° ramp to 220°). Mass spectral data was recorded at 70 eV on a Hewlett-Packard HP-5980A spectrometer. Elemental analyses were made at the Naval Research Laboratory, Washington, DC using a Perkin-Elmer 240A elemental analyzer.

General Procedure for 1-Ethoxyalkynol.- A 1000 ml three-neck, round bottom flask equipped with a Dry Ice condenser, a mechanical stirrer and a gas inlet tube was immersed in an acetone-Dry Ice bath and anhydrous ammonia (600 ml) was introduced. Sodium amide was prepared by the standard technique[9] using 0.5 g hydrated feric nitrate and 37.6 g (1.63 mol) sodium. After the formation of sodium amide was complete, the stopper was replaced by a pressure equalizing dropping funnel containing chloroacetaldehyde diethyl acetal (76.1 g, 0.5 mol) and addition was carried out over a period of 30 min. After 30-60 min, the mixture became light gray. Freshly distilled ketone (0.5 mol) was added rapidly through the addition funnel. The solution was stirred for 2.5 hrs and the ammonia allowed to evaporate overnight. Cautious addition of a saturated ammonium chloride solution (400 ml) with stirring was followed by extraction with 100 ml of ether. CAUTION: 1-Alkoxyalkynols have been reported to be very reactive and occasionally explosive in the presence of trace amounts of acid and it is suggested that all glassware be rinsed with ammonia before use.[9] Two further ethereal extracts (2 X 100 ml) were combined with the original extract and filtered through glass wool to break up the emulsions formed. After removal of any aqueous layer, the ethereal solution dried over anhydrous sodium sulfate, filtered and evaporated in vacuo. Fractional distillation of the residue through a Vigreux column (30 cm) yielded the pure products listed below as clear, colorless liquids.

1-Ethoxy-3-methyl-1-butyn-3-ol (1a), bp. 67-69°/9 mm, lit.[10] bp. 82°/18 mm; IR: 3420 br, 2269 cm^{-1}; ^{1}H-NMR (acetone-d_6): δ 1.32 (t, 3H), 1.41 (s, 6H), 3.97 (s, 1H), 4.03 (q, 2H); MS (m/Z): 128 (M^+, 3%), 113 (100%).

1-Ethoxy-3-ethyl-1-pentyn-3-ol (1b), bp. 62-64°/1.3 mm, lit.[11] bp. 92-93/13 mm; IR: 3480 br, 2230 cm^{-1}; ^{1}H-NMR (acetone-d_6): δ 0.98 (t, 6H), 1.33 (t, 3H), 1.57 (q, 4H), 3.54 (s, 1H), 4.05, (q, 2H); MS (m/Z): 156 (M^+, 7%), 57 (100%).

1-Ethoxy-3-isopropyl-4-methyl-1-pentyn-3-ol (1c), bp. 48-49°/0.2 mm; IR: 3500 br, 2260 cm^{-1}; ^{1}H-NMR (acetone-d_6): δ 0.96 (d, 12H), 1.31 (t, 3H), 1.85 (q, 2H), 3.14 (s, 1H), 4.06 (q, 2H); ^{13}C-NMR (acetone-d_6): 8.27, 10.54, 12.29, 33.88, 68.54, 70.66, 88.10; MS (m/Z): 184 (M^+, 17%), 113 (100%).

Anal. Calcd. for $C_{11}H_{20}O_2$: C, 71.69; H, 10.94

Found: C, 71.37; H, 10.70

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"ONE POT" FISCHER SYNTHESIS OF (2,3,3-TRIMETHYL-3-H-INDOL-5-YL)-ACETIC ACID. DERIVATIVES AS INTERMEDIATES FOR FLUORESCENT BIOLABELS

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(2,3,3-Trimethyl-3-H-indol-5-yl)-acetic acid (3) is expected to possess exceptional advantages as the precursor of a family of dyes of cyanine and related types intended for use as covalently attached fluorescent labels for biological research. In contrast, cyanines utilized previously[1] in such research have not carried a functional group to provide for covalent attachment to proteins. We now describe a convenient synthesis of 3 and its conversion to derivatives used to prepare carboxy cyanines.

Because the hydrazone 2 deteriorated rapidly during storage, attention was directed to "one pot" versions of the Fischer synthesis. However, the procedures listed by Robinson[2] proceeded slowly and gave poor yields of 3. It was found that, in acetic acid, hydrazone formation is nearly complete within 30 minutes in the presence of acetate ion. Indolization to 3 (UV max 260 nm) is essentially complete after 30 minutes at reflux. The generation of small amounts of a purple-red by-product