

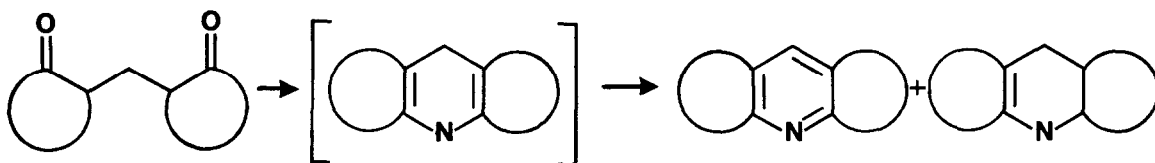
SYNTHESIS OF ANNELATED PYRIDINES FROM 1,5-DIKETONE EQUIVALENTS
USING CUPRIC ACETATE AND AMMONIUM ACETATE

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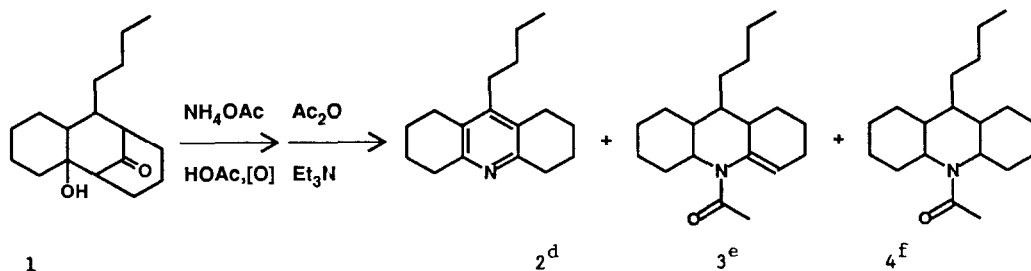
Abstract: Cupric acetate serves as a mild oxidant in the efficient synthesis of 1,2,3,4,5,6,7,8-octahydroacridines 2 and 7 from a 1,5-diketone (6) a ketoalcohol (1) or a 4H-pyran (5) using ammonium acetate in acetic acid.

Pyridines fused to saturated rings are of considerable general interest^{1,2} and are specifically important as structural elements in the architecture of new host compounds³. An effective route to 2,3,5,6-bisannelated pyridines involves the treatment of 1,5-diketones with various ammonia derivatives, including hydroxylamine⁴ and hydrazine⁵. The most popular method for this transformation employs ammonium acetate in refluxing acetic acid, typically yielding the pyridine in 50-70%.^{2,3a,6} As recognized previously,^{6b,c,7} the pyridine product probably arises by disproportionation of the dihydropyridine initially generated by condensation of the 1,5-diketone with ammonium. In this letter we present evidence for the disproportionation mechanism and report that cupric acetate may be used as an oxidant to boost the yield of this reaction above 95%.



As previously reported,^{3a} ketoalcohol 1 may be converted in 32% to 9-n-butyl-1,2,3,4,5,6,7,8-octahydroacridine (2, Table) by treatment with hydroxylamine hydrochloride in acetic acid. The importance of this product as a building block for construction of preorganized host compounds^{3b,c} led us to search for a more efficient method that also would be feasible on a large scale. Since ketoalcohol 1 is related to the isomeric 1,5-diketone by a retro-aldol process, condensation with ammonium acetate in acetic acid should afford the bisannelated pyridine 2. Indeed, 2 was obtained in fair yield, but it was accompanied by pyrrolidine and piperidine side products that could be removed by acetylation and extraction. The first entry of the Table shows that, although conversion was incomplete, N-acetyldodecahydroacridine 3 and N-acetyltetradecahydroacridine 4 were isolated in 10% and 5% yield, respectively. When 70 mole % CrO₃ was added to the reaction mixture, the yield of 2 was increased to 67%, but tarry by-products made large-scale purification of the product difficult.⁸

TABLE. REACTION OF 8-*n*-BUTYL-2-HYDROXYTRICYCLO[7.3.1.0^{2,7}]DODECAN-13-ONE WITH AMMONIUM ACETATE IN REFLUXING ACETIC ACID.^a



Oxidant[O]	Time (hours)	Yield (%)	Yield (%)	Yield (%)
None ^b	2.0	42	10	5
Air ^c	0.75	60	15	6
Oxygen ^c	0.25	55	5	3
Air ^c + 20 mole % Cu(OAc) ₂	1.75	86	0	0
Air ^c + 110 mole % Cu(OAc) ₂	2.0	>95	0	0
250 mole % Cu(OAc) ₂ ^b	2.0	>95	0	0

a) All reactions were conducted using 9 mmoles of 1 and 28 mmoles of ammonium acetate in 15 mL of acetic acid, heated under reflux for the specified time. Workup was performed by cooling the reaction mixture to 0°C, diluting with water, basification with 50% aq. NaOH and extraction with diethyl ether. The resulting product mixture was heated with 2.5 equivalents of acetic anhydride and 2.5 equivalents of triethylamine at reflux under nitrogen for 1 hour. Volatile materials were evaporated *in vacuo* and the residue was dissolved in ether and extracted with pH 3.75 buffer. Octahydroacridine 2^d was liberated from the aqueous extract by basification and extraction with ether. Acetamides 3^e and 4^f were not extracted into pH 3.75 buffer and were isolated by evaporation of the ether layer, followed by column chromatography on silica gel with ethyl acetate/hexanes elution. All yields refer to spectroscopically pure products isolated by these methods.

b) Reaction conducted under nitrogen.

c) Gas ebullition rate approximately 25 mL/min.

d) This product was identical to samples prepared previously,^{3a} according to comparison of melting point (37-38°C), tlc properties and IR and ¹HNMR spectra.

e) ¹HNMR (300 MHz, CDCl₃) δ 0.95 (t, 3H), 1.1-2.29 (m, 26H), 4.25 (q, 1H), 4.90 (t, 1H); IR (film) 2930, 2860, 1625, 1410, 1215 cm⁻¹; MS m/z 289 (M+).

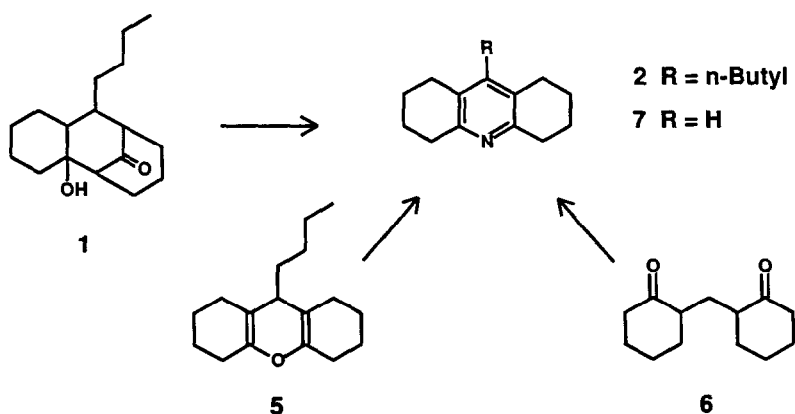
f) ¹HNMR (300 MHz, CDCl₃) δ 0.95 (t, 3H), 1.0-2.9 (m, 27H), 4.3 (m, 2H); IR (film) 2940, 2860, 1615, 1415, 1220 cm⁻¹; MS m/z 291 (M+).

We have examined a number of additives as potential oxidants for the dihydropyridine intermediate in the conversion of 1 to 2. As shown in the Table, constant bubbling of air into the reaction mixture does not significantly decrease products 3 and 4. Bubbling oxygen does decrease these reduced pyridines, but the formation of tarry by-products becomes a problem. In an attempt to catalyze air oxidation of the intermediate, we employed 0.2 molar equivalents of cupric acetate monohydrate and obtained a high yield of *n*-butyloctahydroacridine 2, that was free from reduced products 2 and 3. Remarkably, the reaction is nearly quantitative when 1.1 molar equivalents of cupric acetate is used. With 2.5 molar equivalents of cupric acetate the reaction may be conducted under nitrogen and the product is free from colored impurities formed in the presence of air.

To explore the utility of our procedure, we examined the conversion of other 1,5-diketone equivalents to annelated pyridines, as shown in the chart below. Thus, treatment of 4H-pyran 5⁹ or 2,2'-methylenebiscyclohexanone (6)¹⁰ with 2.5 molar equivalents of cupric acetate and 3 molar equivalents of ammonium acetate in refluxing acetic acid for 2.5 to 3 hours yielded 93-94% of octahydroacridine 2 or 7,¹¹ respectively. These reactions are amenable to large scale (40-50 g) because copper salts are readily removed by extraction with aqueous ammonium chloride and ammonium hydroxide, and no observable by-products are formed.

Cupric acetate plays a crucial role as a selective oxidant in these reactions. When 5 was treated with ammonium acetate in the absence of cupric acetate, none of the pyridine (2) was detected, suggesting that 5 might be oxidized directly to the pyrylium salt, which would readily afford the pyridine under these conditions.¹² Cupric acetate has also been employed as a catalyst in the low yield oxidative conversion of 3,4-dihydro-2H-pyrans to pyridines.¹³ Whereas copper(II) may be used as an air-oxidation catalyst in the synthesis of octahydroacridines from 1,5-diketone equivalents, higher product purity makes stoichiometric copper(II) more attractive for many applications.

CHART. CONVERSION OF 1,5-DIKETONE EQUIVALENTS TO 1,2,3,4,5,6,7,8-OCTAHYDROACRIDINES USING CUPRIC ACETATE AND AMMONIUM ACETATE IN ACETIC ACID.



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