

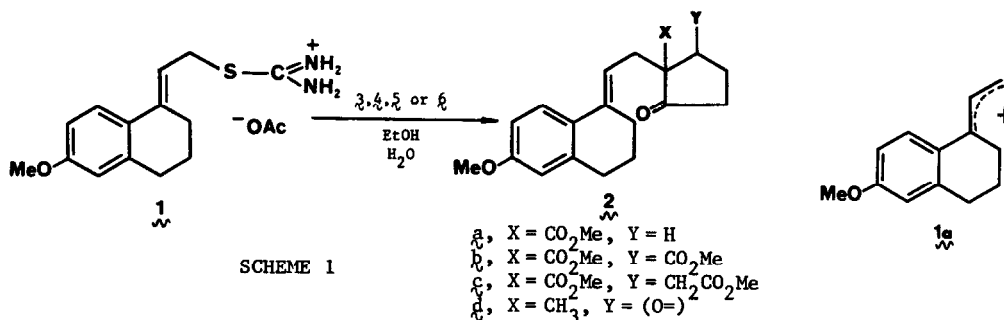
STEROIDS I. ALKYLATION OF β -KETOESTERS VIA THEIR Cu(II) ENOLATES IN AQUEOUS MEDIA.
 APPLICATION TO THE SYNTHESIS OF C-18 FUNCTIONALIZED STEROIDS VIA THE TORGOV APPROACH.

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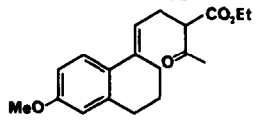
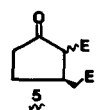
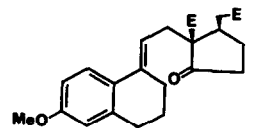
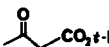
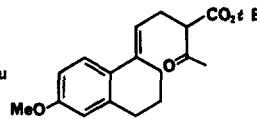
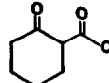
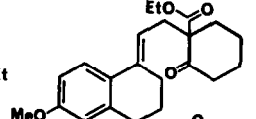
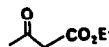
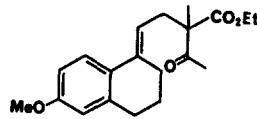
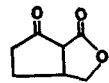
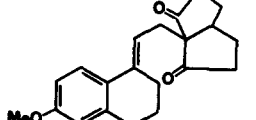
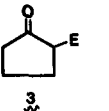
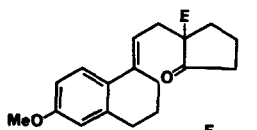
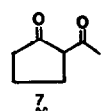
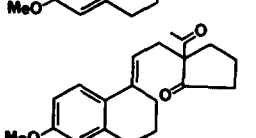
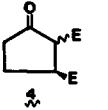
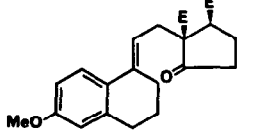
Abstract. Three steroidal pentaenes (**3a-c**) have been synthesized, the key step being the alkylation of the Cu(II) chelates of the ring D precursors (**3-5**) by the iso-thiouronium acetate **1** in aqueous solution.

Although the key alkylation-condensation step of the modified¹ Torgov synthetic approach² to estrone is highly efficient with 2-methylcyclopentane-1,3-dione (**6**) as the nucleophile (90% yield of **2d**), the reaction affords very low yields (0-15%) of tricyclic products (**2a-c**) when the corresponding cyclic β -ketoesters (**3-5**) are employed as the substrates³ (Scheme 1).



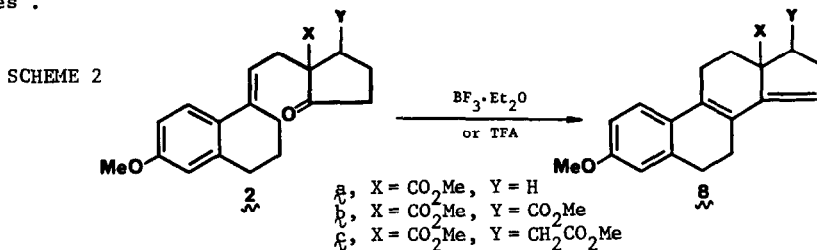
We reasoned that the diminished reactivity of the β -ketoesters was due to their higher pKa values compared with that (pKa⁴4.5) of **6** which has been shown to be the acid catalyst for the condensation¹. On the contrary neither base catalysis (DMAP, Et₃N) nor the use of activated substrates (β -ketothioesters⁴) improved the yield of the desired alkylation. It seems that the presence of specific concentrations (so far undefined) of the β -ketoester enolate and probably the cation **1a** are necessary if coupling is to occur, conditions which obviously we failed to satisfy in these attempts. However by addition of 1.0 eq. of copper(II) acetate to the simple reaction mixture we were able to isolate a 45% yield of **2a**. Furthermore, when the reaction mixture was buffered with 0.1 M NaOAc the yield of pure **2a** increased to 66%. Table I establishes the generality of this Cu(II)-promoted alkylation.

TABLE I

Entry ^a	β -ketoester ^{b,e}	Product ^c	% Yield ^d	Entry ^a	β -ketoester ^{b,e}	Product ^c	% Yield ^d
1.			58	6.			45
2.			53	7.			51
3.			10	8.			0
4.			66 ^f	9.			74
5.			61				

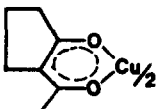
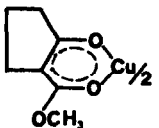
- a. Entry 9, even though a β -diketone, was included since in the absence of Cu(II) only a 40% yield of the coupled product was obtained.
- b. The symbol E represents $-\text{CO}_2\text{Me}$.
- c. All products have been fully characterized by spectral data (^1H and ^{13}C N.M.R., I.R. and U.V.) and their elemental composition established by high resolution mass spectroscopy.
- d. Refers to isolated, pure products (by G.C., SP 2100 column, 180–270°C, 2 min delay, 8°C/min). Yields based on recovered \downarrow were higher by 15–30% in all entries except 3 and 8.
- e. 1.3–1.5 eq. were used relative to \downarrow .
- f. Ni(II) acetate afforded a slightly higher yield (72%). Cu(I) bromide gave similar results.

Cyclic and acyclic β -ketoesters participate equally well with the exception of entry 3 which surprisingly⁵ gives a very low yield and the substrate of entry 8 which is completely inert in accordance with its reluctance to enolize. The stereochemistry assigned to the tricyclic products in entries 5 and 6 is based on the usual arguments of a) steric approach control during alkylation⁶ and b) allylic strain⁷, and is supported to a limited degree by chemical studies⁸.



Compounds **2a**, **2b** and **2c** (products in entries 4-6) were cyclized under acidic conditions to give the corresponding crystalline pentaenes⁹ (**8a-c**, 74-80% yields), precursors to a series of, so-far, inaccessible C-18 functionalized steroids¹⁰, the ultimate goal of our research (Scheme 2).

With regard to the mechanism of the key coupling reaction it seems likely that the Cu(II) chelates of the 1,3-dicarbonyl compounds are intermediates. To test this hypothesis we prepared¹² the corresponding Cu(II) complexes of **3** and **7** and studied their reaction with **1** in aqueous ethanol (1:1). The results are summarized in Table II.

TABLE II	Cu(II) salt ^a	1.0 eq.	1.0 eq.	2.0 eq.
		No NaOAc	0.1M NaOAc	0.1M NaOAc
	15^b	40	68	
	12	36	61	

a. Dried over P_2O_5 , crude salts.

b. All numbers refer to isolated pure products as in entries 4 and 9 of Table I.

Two consequences emerge from Table II. First, that the Cu(II) chelates are indeed intermediates and second, that buffered solutions (faintly alkaline) are mandatory for high yields. The latter can be rationalized in view of the efficient formation^{12b} and relative stability¹³ of metal β -ketoenolate complexes in non-acidic media. According to further studies that we have made the role of Cu(II) is not catalytic, an effect that may be due to the formation, irreversibly, of a copper-sulfur bond during the reaction. The questions as to whether the alkylation occurs on a free or on a metal bound enolate^{13a,14} and what is the exact fate of Cu(II) during the reaction will be the subject of further mechanistic studies.

In summary these results represent the first synthetically useful alkylation of well-defined^{15,16} Cu(II) chelated enolates¹⁷ in aqueous media¹⁸. Promotion of the alkylation shown in Scheme 1 by other metals is under study as is the use of η -allyl Pd(0) complexes¹⁹ of **1a** as an alternate approach to the synthesis of estrone-like compounds. These results will be reported in due course.

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References and Notes

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8. In each case only one diastereomer was detected by ^{13}C -M.R. spectroscopy. Cyclization of **2b** to the pentaene **8b** followed by catalytic hydrogenation (Pd/CaCO_3 , pyridine) affords a single diastereomer which is expected from a cis relationship of the two ester functions.
9. Melting points were as follows: **8a**, 122-124°C; **8b**, 140-142°C; **8c**, 112-113°C.
10. We have completed the synthesis of a series of C-18 functionalized steroids via **8a** which was also synthesized via the somewhat lengthy Smith-Hughes approach¹¹. R. Pillai, I. Shoshani, W.V. Murray, K.H. Tseng, P.A. Magriotis and F. Johnson, manuscript in preparation.
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