for a cation having twice the thickness of a normal metallointercalator.[3] From an examination of space-filling models of **2** and the DNA double helix it is apparent that base pair displacement would have to occur to accommodate intercalative binding of the bis[terpyridineplatinum(II)] reagent. The triplatinum(II) complex might therefore be used to identify base substitution mutations.[12] Because of its high electron density, it might also prove to be useful in preparing heavy-atom derivatives of biological molecules.

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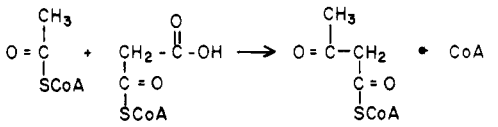
Copper(I) Promoted Acylation Reactions. A Transition Metal Mediated Version of the Friedel–Crafts Reaction

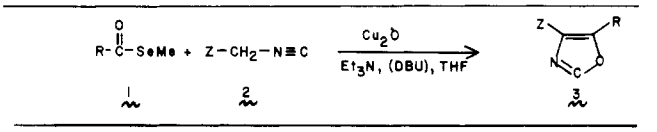
Sir:

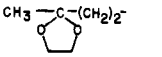
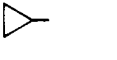
Thioesters of coenzyme A are important intermediates in carboxylic acid metabolism. They serve as "activated" acid derivatives, keying, for example, the important carbon–carbon-bond-forming reaction in the synthesis of acetoacetyl CoA.[1]



Studies conducted in our laboratories have now revealed that selenol esters[2] can, in analogy to the actual role played by thioesters in the biochemical process cited above, be used in carbon–carbon-bond-forming reactions. This work was originally initiated to achieve a new synthesis of 2-unsubstituted oxazoles. We had envisaged that selenol esters could replace acid chlorides in the assembly of these heterocycles from activated isonitriles, if these reactions were conducted in the presence of a soft metal ion showing a strong affinity for selenium. This process would thus serve as a useful modification to the standard Schöllkopf oxazole synthesis.[3]

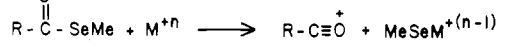
Table I. Synthesis of 2-Unsubstituted Oxazoles



1 (R)	2 (Z)	Base	Reaction Time (h)	Isolated Yield (%)
ø-	CO_2Et	Et_3N	14	60
	CO_2Et	Et_3N	11	92
	CO_2Et	Et_3N	6	61
$CH_3(CH_2)_8$-	CO_2Et	Et_3N	12	85
$CH_3(CH_2)_8$-	Tos	DBU	20	40

Our hopes were nicely realized, for simply stirring the selenol ester and isonitrile (Z = CO_2Et or Tos) at room temperature for 6–20 h in the presence of 1.5 equiv of Et_3N or DBU and 1.5 equiv of anhydrous cuprous oxide affords in good yield the 2-unsubstituted oxazole **3** by a process presumably proceeding through an intermediate β-ketoisonitrile (Table I). The cuprous oxide functions as an efficient reagent for complexation to the selenium moiety.

With this information in hand, we now considered the possibility that selenol esters might be able to participate in other processes, such as the Friedel–Crafts acylation of aromatics, thus providing a new source of oxocarbenium ions. We imagined that a system could be properly designed which might allow acylation reactions to proceed under relatively mild (neutral) conditions using metal salts which did not possess the high Lewis acidity characteristic of the main group catalysts. Again, one would rely on a soft-soft-type metal–selenium interaction to key the desired bond-forming process.[4]



While our previous studies had revealed that Hg(II) and Cu(II) salts were effective for the conversion of selenol esters to amides, esters, and acids,[2] we found these salts to be ineffectual in the attempted acylation of the electron-rich aromatic anisole in benzene or THF as solvent. Although mercuric trifluoroacetate and cuprous trifluoroacetate offer the advantage of being partially soluble in organic solvents, these salts led only to partial conversion of the selenol ester into its corresponding acid. No traces of the desired acylation products could be detected. Heterogeneous reaction mixtures using mercuric chloride, silver nitrate, cupric chloride, and cuprous oxide were also examined, but again acylation of anisole was not observed.

In contrast, use of the highly reactive crystalline complex of copper(I) triflate and benzene [$(CuOTf)_2PhH$], a reagent first described by Kochi and Salomon, does readily induce the desired transformation.[5] The reaction (entry 6, Table II), which was complete within minutes at room temperature in benzene as solvent, afforded an 81% isolated yield of the acylated product which was found to consist of >95% para isomer by VPC and ^1H NMR analysis. Other examples of this process are displayed in Table II.

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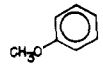
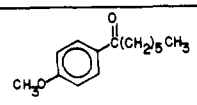
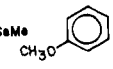
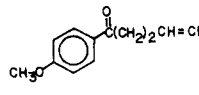
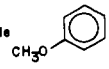
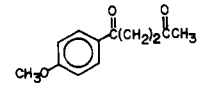
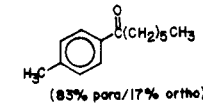
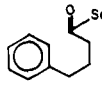
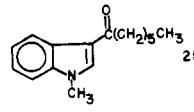
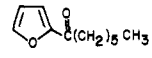
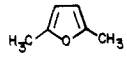
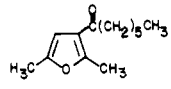
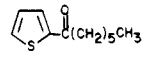
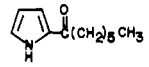
Table II. Cu(I) Promoted Acylations

Entry	Selenol Ester	Aromatic Compound	Product[a]	Reaction Time(min)	Isolated[b] Yield (%)
6	$CH_3(CH_2)_5COSeMe$			40	81
7	$CH_2=CH-(CH_2)_2COSeMe$			15	55
8	$CH_3CO(CH_2)_2COSeMe$			3	60
9	$CH_3(CH_2)_5COSeMe$		 (83% para/17% ortho)	150	28
10				5	70
11	$CH_3(CH_2)_5COSeMe$			25	85
12	$CH_3(CH_2)_5COSeMe$			15	100
13	$CH_3(CH_2)_5COSeMe$			10	91
14	$CH_3(CH_2)_5COSeMe$			20	81
15	$CH_3(CH_2)_5COSeMe$			15	64

[a] Satisfactory NMR, IR, and high resolution mass spectral data were obtained for all compounds. [b] Purification was accomplished by bulb-to-bulb distillation in all cases.

Toluene (entry 9) could be acylated in only low yield with the Cu(I)–selenol ester system on employing it as the reaction solvent. This compound appears to represent the lower limit of arene reactivity required to observe acylation, for arenes possessing more powerful electron-withdrawing groups (e.g., methyl benzoate) failed to give detectable amounts of acylation products. It is also relevant to note that methylthiol esters react only sluggishly under these conditions.

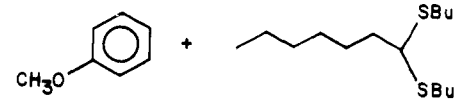
Intramolecular acylation was effected in high yield as revealed in the preparation of α-tetralone (entry 10; the 1-indanone could not be prepared in an analogous fashion). Heterocyclic compounds such as furan, thiophene, pyrrole, and *N*-methylindole readily underwent acylation in near-quantitative yield under the standard conditions.

An exemplary procedure using *N*-methylindole as the acylation substrate is the following. Into a 10-mL side-armed flask equipped with an argon filled balloon was placed 254 mg (0.50 mmol) of the cuprous triflate–benzene complex. Dry benzene (5 mL) and 54.7 mg (0.42 mmol) of *N*-methylindole were added. The selenol ester prepared from methyl heptanoate (104 mg, 0.50 mmol) was then added neat to this pink-colored reaction mixture. After 25 min, the now clear, red-colored solution was diluted with 30 mL of ether, washed with 6 M NH_4OH (2 × 10 mL), dried, and concentrated. Bulb-to-bulb distillation of the residue (125–130 °C oven temperature, 0.4 mm) afforded 77 mg (85%) of the 3-acylated indole: IR (thin film) 1650 cm^{-1}; NMR (CCl_4) δ 8.17–8.47 (m, 1 H), 7.44 (s, 1 H), 7.00–7.37 (m, 3 H), 3.71 (s, 3 H), 2.63 (t, 2 H, J = 7.0 Hz), 0.53–2.00 (br m, 11 H); MS *m/e* (M^+) 243.1625.

Since triflic acid is produced as a byproduct of this acylation process, attempts were made to perform the reaction in the presence of various amine bases (proton sponge, Hünig's base, 2,6-lutidine, 1,1,3,3-tetramethylurea, and 2,6-di-*tert*-butyl-4-methylpyridine) which could serve to remove this very strong acid from solution.[7] All of these attempts were unsuccessful, for the amines blocked the activity of the copper reagent presumably through preferential σ or π complexation of amine base to copper. Only with calcium carbonate present was acylation of anisole still found to occur. The generation of triflic acid does not, however, appear to be serious, for acylation of the acid-sensitive substrate furan does proceed in high yield as previously noted.

It is important to emphasize that these copper-promoted acylation reactions differ mechanistically from the classical Friedel–Crafts reaction in that the former probably involves oxocarbenium ion formation through complexation of metal to the departing anionic group. The latter process, however, arrives at presumably the same intermediate, but through a sequence involving initial complexation by the hard metal (e.g., $AlCl_3$) to the hard carbonyl oxygen.[8]

As might be anticipated based on the foregoing results, this highly reactive cuprous triflate complex should also be useful for promoting alkylations of aromatics by dithioacetals. We investigated this possibility in only a single instance. When the dithioacetal of *n*-heptanal **4** was reacted with cuprous triflate and anisole under conditions similar to those described for the acylation reaction, an 80% yield of alkylation products **5** was obtained. Alkylations of other reactive aromatics should be equally feasible.[9]



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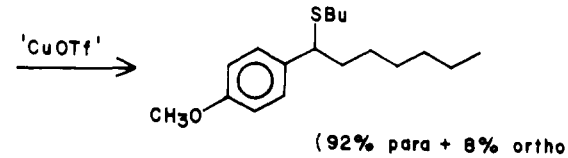

5

In summary, we believe that the relatively unique procedure for the acylation of aromatics reported herein provides a useful alternative to the classical Friedel–Crafts reaction. Additional experiments using more complex molecules will, however, be required to establish the general utility of this process in synthetic organic chemistry.

Acknowledgment. The authors are indebted to the Health Research and Services Foundation of Pittsburgh, Pa., and the National Institutes of Health (Grant No. R01 HL2059-03) for support of these investigations. The technical assistance of Alexander Vasilakis is also gratefully acknowledged.

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(7) Attempts to effect acylation using selenol ester and triflic acid were unsuccessful, thus demonstrating that this is not an acid-catalyzed process.
(8) B. Chevrier and R. Weiss, *Angew. Chem., Int. Ed. Engl.*, **13**, 1 (1974); P. H. Gore, *Chem. Ind. (London)*, 727 (1974).
(9) Substitution products have been observed for anisole and bivalent sulfur compounds using Cu(II) salts: T. Mukaiyama, K. Narasaka, K. Maekawa and H. Hokonoki, *Bull. Chem. Soc. Jpn.*, **43**, 2549 (1970). Cuprous trifluoromethanesulfonate has previously been used to generate sulfur stabilized carbonium ions from thioacetals and thioketals: T. Cohen, A. J. Mura, D. W. Shull, E. R. Fogel, R. J. Ruffner, and J. R. Falck, *J. Org. Chem.*, **41**, 3218 (1976), and references cited therein. Also see B. M. Trost, M. Reiffen, and M. Crimmin, *J. Am. Chem. Soc.*, **101**, 257 (1979).
(10) Fellow of the Alfred P. Sloan Foundation.

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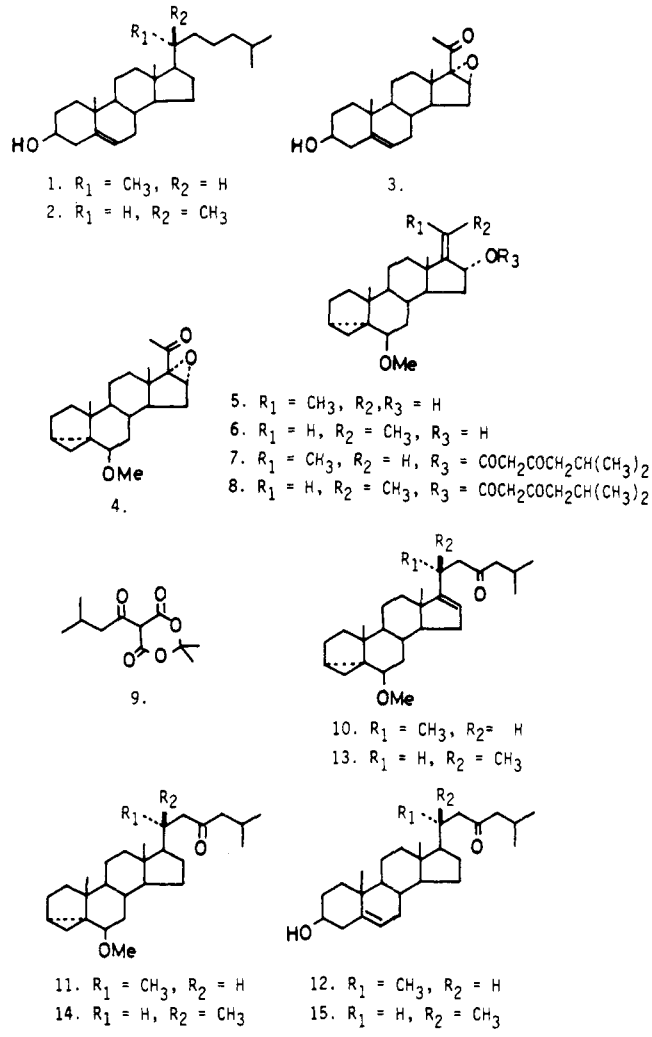
Stereocontrolled Synthesis of Sterol Side Chains†

Sir:

The recent discovery from marine and animal sources of many new sterols[1] with novel side-chain structures has focused attention on developing stereocontrolled methods to introduce these side chains onto tetracyclic steroidal starting materials. An important problem that arises from this approach is the stereospecific control of the C-20 stereochemistry. Many previous attempts[2] to control this center have relied upon catalytic hydrogenation of $\Delta^{17(20)}$ or $\Delta^{20(22)}$ olefins which have invariably led to an epimeric mixture of 20*R* and 20*S* isomers.[3,4]

To exemplify our approach we report on a highly stereocontrolled synthesis of either cholesterol (**1**) or 20-isocholesterol (**2**) from the readily available 16α,17α-epoxy-20-ketopregnane derivative (**3**) that relies on a Claisen rearrangement for stereocontrol of the C-20 center. Protection of **3** as the 3α,5α cyclo ether derivative (**4**) followed by Wharton reaction[5] with hydrazine in *N,N*-dimethylethanolamine yielded a crystalline allylic alcohol (**5**, 63%) [mp 108–110 °C; $[\alpha]_D$ +19°; NMR 0.91 (s, 3 H, C-18 Me), 1.03 (s, 3 H, C-19 Me), 1.73 ppm (d, J = 7 Hz, 3 H, C-21 Me)] and an oil isomer (**6**, 27%) [$[\alpha]_D$ +33°; NMR 0.77 (s, 3 H, C-18 Me), 1.03 (s, 3 H, C-19 Me), 1.79 ppm (d, J = 7 Hz, 3 H, C-21 Me)] which were separated by crystallization.[6] Assignment of the 17(20) *E* olefin stereochemistry to the crystalline isomer (**5**) and the 17(20) *Z* configuration to the minor isomer (**6**) was achieved by correlation of the C-18 methyl shifts in the ^{1}H NMR in accord with Benn's earlier observations.[7]

As pointed out in many reviews on the Claisen rearrangement[8] reaction, a highly ordered six-membered transition state in the concerted cyclic process accounts for the high stereoselectivity observed. From examination of the respective

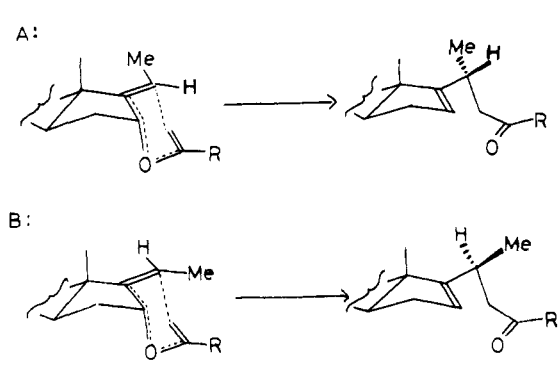


Claisen rearrangement transition states A and B for the two allylic alcohols (**5** and **6**) (Scheme I), it was reasoned that the *E* isomer **5** would give the natural (20*R*) configuration at C-20 and the *Z* isomer **6** would yield the unnatural C-20 isomer. This strategy was successfully realized with the Carroll variant[9] of the Claisen rearrangement on the respective allylic β-ketoacetates **7** and **8**.

The key allylic β-ketoacetates were prepared by taking advantage of Yonemitsu's[10] recent findings that 5-acyl Meldrum's acid, 2,2-dimethyl-1,3-dioxane-4,6-dione derivatives, react with allylic alcohols (1 h in refluxing xylene) to afford β-ketoacetates. The 5-isovaleryl Meldrum's acid (**9**) in turn was prepared by pyridine-catalyzed acylation of Meldrum's acid with isovaleryl chloride.

Carroll reaction of the ester **7** in boiling xylene yielded after 2.5 h in 90% yield a single rearranged material,[11] characterized

Scheme I



Dedicated to Professor Tetsuo Nozoe on the occasion of his 77th birthday.

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