mined by measurement of the ultraviolet extinction coefficient at the 282-mμ maximum[1] and liquid scintillation counting[7] of an aliquot. A value of 1.44 Ci/mole was thus obtained, showing that an isotope effect had taken place during one or more of the steps in this conversion.

Experiments are now in progress in our laboratory to demonstrate the metabolic fate of (−)-$\Delta^{1(6)}$-THC in several laboratory animal species. Results thus far indicate that this method of labeling is satisfactory for such studies.

(7) The samples were counted in a Nuclear-Chicago Mark I counter; efficiencies were determined by the channels ratio method.

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Thallium in Organic Synthesis. I. Alkylation and Acylation of β-Dicarbonyl Compounds[1]

Sir:

Monoalkylation at carbon of β-dicarbonyl anions is a superficially prosaic process which, however, often competes with dialkylation at carbon, O-alkylation (formation of enol ethers), β-diketone cleavage, Claisen condensations, and coupling resulting from air oxidation of the enol salts of both the starting β-dicarbonyl compound and its monoalkylation product. As a consequence, careful fractional distillation of the resulting agglomerate (which may also contain unchanged starting material as well) is usually necessary for the isolation of the desired monoalkylation product.

We wish to describe a method for the monoalkylation of β-dicarbonyl compounds which gives the C-alkylated product in essentially quantitative yield under neutral conditions and which avoids *all* of the above-mentioned competitive reactions. The thallium(I) salt of the β-dicarbonyl compound is heated with an excess of an alkyl iodide, the thallium(I) iodide removed by filtration, and the product isolated by simple distillation.[2] Representative examples, reaction conditions, and yields are given in Table I. The products in all cases are vpc pure as isolated.[3]

The requisite thallium(I) salts are readily prepared in a number of ways, the simplest of which we have found to be the addition of thallium(I) ethoxide[4] to a solution of the β-dicarbonyl compound in an inert solvent such as benzene or petroleum ether. The thallium(I) salt crystallizes from the solution almost immediately and is collected by filtration and recrystallized, usually from ethanol. These salts are formed in quantitative yield and are beautifully crystalline, stable, nonhygroscopic, sharp melting solids which may be stored indefinitely. They may alternatively be prepared by the use of thallium(I) hydroxide in aqueous solution (*cf.* ref 3) or by direct exchange of thallium between the β-dicarbonyl compound and cyclopentadienylthallium(I);[5] the reaction is irreversible because of the formation of cyclopentadiene. Since this method avoids even traces of base, it is potentially suitable for the preparation of thallium(I) salts even from extremely base-sensitive substrates.

Table I. Mono-C-alkylation of Thallium(I) Salts of β-Dicarbonyl Compounds

Tl^+ salt of	Yield, % (hr), with CH_3I	CH_3CH_2I	$(CH_3)_2CHI$
Ethyl acetoacetate	100 (4)	100 (4)	91 (15)
Acetylacetone	100 (4)	93 (16)	90 (14)
2-Carbethoxycyclopentanone	100 (9)	100 (9)	96 (12)
Ethyl benzoylacetate	100 (4)	100 (4)	99 (22)
Ethyl 2-methylbenzoylacetate	100 (14)	92 (14)	93 (14)

The resulting monoalkylated β-dicarbonyl compounds may, in turn, be converted to their respective thallium(I) salts which may then be alkylated with a second alkyl halide. Both reactions are again quantitative. A representative example is given in Table I.

The thallium(I) salts of β-dicarbonyl compounds may be acylated as well as alkylated, and this reaction can be controlled to give O- or C-acylation. For example, the thallium(I) salt of acetylacetone upon treatment with acetyl chloride at −78° gives the enol acetate in >90% yield. However, treatment with acetyl fluoride at room temperature gives triacetylmethane in >95% yield. The latter compound may be converted in turn to its thallium(I) salt; alkylation with methyl iodide gives 1,1,1-triacetylethane in >95% yield. This compound may alternatively be prepared by acylation of the thallium(I) salt of 3-methylpentane-2,4-dione with acetyl fluoride.

The experimental conditions for acylations are essentially the same as for the alkylations cited above. The thallium(I) salt is suspended in ether and treated with the appropriate acylating agent. Thallium(I) halide is removed by filtration and the product isolated by simple distillation. Representative examples are given in Table II.

The crystal structure of a representative thallium(I) salt (acetylacetonatothallium(I)) has been determined.[6] It is a 1:1 complex; although one can pick out a discrete molecular unit in which a thallium atom is bonded to the two oxygen atoms of one acetylacetone ligand (Tl–O distances of 2.43 and 2.54 Å),[7] each thallium

(1) We gratefully acknowledge the financial support of this work by the Smith Kline and French Laboratories, Philadelphia, Pa.

(2) Alkyl bromides may also be used, but since they are less reactive than the iodides higher reaction temperatures and/or the use of a catalyst (*e.g.*, triethylamine) may be required, with a resulting small decrease in yield.

(3) Our attention was originally drawn to the possible synthetic potential of this reaction by an observation reported by R. C. Menzies and E. M. Wilkins (*J. Chem. Soc.*, 1151 (1924)) that the thallium(I) salt of ethyl acetonedicarboxylate was "readily soluble in cold ethyl or methyl iodide, thallous iodide being deposited on standing or on heating." Although Menzies later reported (C. M. Fear and R. C. Menzies, *J. Chem. Soc.*, 937 (1926)) apparent C-ethylation of the thallium(I) salt of ethyl acetoacetate in moderate yield, the structure of the product was not established, and the synthetic potential of the method was not recognized.

(4) G. Brauer, Ed., "Handbook of Preparative Inorganic Chemistry," Vol. 1, 2nd ed, Academic Press Inc., New York, N. Y., 1963, p 877.

(5) Methods available for the preparation of cyclopentadienylthallium(I) are summarized in A. N. Nesmeyanov and R. A. Sokolik, "Methods of Elemento-Organic Chemistry. Volume I. The Organic Compounds of Boron, Aluminum, Gallium, Indium and Thallium," The World Publishing Co., New York, N. Y., 1967.

(6) We are indebted to Dr. Ned C. Webb, The Procter and Gamble Co., Cincinnati, Ohio, for the X-ray determination. Full details on this structure will be published independently.

(7) Both ir and nmr spectra confirm O–Tl–O bonding. The complexes show no carbonyl band, but a C=C stretching band appears at 1630–1650 cm^{-1}. A single vinyl C–H signal is observed in all the complexes as a sharp singlet at about τ 4.5.

atom is bonded to oxygen atoms of neighboring molecules in such a way that molecules are linked indefinitely along the *a* and *c* axes, but not along *b*. The oxygen and thallium atoms are buried within the interior of the crystals with a consequent exposure of the carbon backbone of acetylacetone units at the crystal surface. It is attractive to postulate that the extraordinary specificity observed in alkylation and acylation reactions may be directly related to the crystal structure of the complexes and to the rigid geometry imposed on the transition states for reaction as a consequence of the tetragonal-pyramidal structure of the tetracoordinate thallium complex. Certainly heterogeneity in the above reactions is a critical requirement for specificity. Further speculations at this time on the relevance of structure to chemical reactivity and specificity, however, would be premature.

Table II. Acylation of Thallium(I) Salts of β-Dicarbonyl Compounds

Tl^+ salt of	Yield, %, of O-Acetyl derivative[a]	Yield, %, of C-Acetyl derivative[b]
Ethyl acetoacetate	90	95
Acetylacetone	90	95
2-Carbethoxycyclopentanone	90	95
Ethyl benzoylacetate	90	98
3-Methylpentane-2,4-dione	95	95

[a] Prepared by treatment of the salt in ether with acetyl chloride at −78°. [b] Prepared by treatment of the salt in ether with acetyl fluoride at room temperature.

Representative experimental procedures are as follows. **Acetylacetonatothallium(I):** Acetylacetone (0.11 mole) is stirred in 50 ml of petroleum ether and 0.10 mole of thallium(I) ethoxide added all at once. The mixture is stirred for 2–3 min, chilled, and filtered; the yield of acetylacetonatothallium(I) is quantitative; mp 160.5°.[8-10] **3-Methylpentane-2,4-dione:** A suspension of 0.10 mole of acetylacetonatothallium(I) in 85 ml of methyl iodide is heated under reflux with stirring for 4 hr, cooled, and filtered. The filtrate is passed through a short column of Florisil to remove traces of thallium(I) iodide, concentrated, and distilled (68–70° (26 mm)). The yield is quantitative. **Triacetylmethane:** Acetyl fluoride is bubbled into a suspension of 0.10 mole of acetylacetonatothallium(I) in 200 ml of ether at a rate of 0.2 l./min for 30 min. The thallium(I) fluoride is removed by filtration and the filtrate concentrated and distilled (95–97° (1.0 mm)). The yield of triacetylmethane is >95%.

(8) E. Kurowski, *Ber.*, 43, 1078 (1910).
(9) G. H. Christie and R. C. Menzies, *J. Chem. Soc.*, 2372 (1925).
(10) G. T. Morgan and H. W. Moss, *ibid.*, 195 (1914).

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Thallium in Organic Synthesis. II. Acylation, Aroylation, and Tosylation of Phenols and Carboxylic Acids[1]

Sir:

Thallium(I) salts of phenols are readily prepared in quantitative yield by the addition of thallium(I) ethoxide[2] to a solution of the phenol in a solvent such as benzene or ethanol. They are crystalline, sharp-melting, stable solids which may be conveniently recrystallized from water or aqueous ethanol.[3-5] We have found that treatment of a suspension of these phenol salts in anhydrous ether with an equimolar quantity of an acyl or aroyl halide for 1 hr at room temperature, followed by filtration of the thallium(I) halide and evaporation of solvent, affords pure phenol esters in yields seldom lower than 97%. In every case investigated this procedure is the method of choice. Representative examples are given in Table I.

Table I

$$ROTl + R'COCl \longrightarrow R'COOR + TlCl$$

R	Yield, %, for R′ = CH_3	Yield, %, for R′ = $(CH_3)_3C$	Yield, %, for R′ = C_6H_5
C_6H_5	98	96	98
p-$NO_2C_6H_4$	98	100	100
o-$CHOC_6H_4$	98	83	97
p-$CH_3OC_6H_4$	100	98	100
β-$C_{10}H_7$	96	97	97

Treatment of the thallium(I) salts of phenols with tosyl chloride in dimethylformamide or dimethylacetamide for 15 min at room temperature, removal of thallium(I) chloride by filtration, and dilution of the filtrate with water, followed by extraction with benzene and evaporation, gives crystalline phenol tosylates in 92–96% yield. Representative conversions are given in Table II.

Table II

$$ROTl + TsCl \longrightarrow ROTs + TlCl$$

R	Yield, %
C_6H_5	96
p-$NO_2C_6H_4$	95
o-$CHOC_6H_4$	92
o-$CH_3OC_6H_4$	94

Thallium(I) salts of carboxylic acids can also be readily prepared in quantitative yield by the addition of thallium(I) ethoxide to a solution of the acid in a suitable solvent such as ether or ethanol. These salts are crystalline, light-insensitive, sharp-melting, stable solids.[3] We have found that treatment of these thallium(I) carboxylates in ether suspension with a stoichiometric amount of an acyl or aroyl chloride, removal of thallium(I) chloride by filtration, and evaporation of the ether solvent at <30° afford carboxylic anhydrides in

(1) We gratefully acknowledge the financial support of this work by the Smith Kline and French Laboratories, Philadelphia, Pa.
(2) G. Brauer, Ed., "Handbook of Preparative Inorganic Chemistry," Vol. 1, 2nd ed, Academic Press Inc., New York, N. Y., 1963, p 877.
(3) R. C. Menzies and E. M. Wilkins, *J. Chem. Soc.*, 125, 1148 (1924).
(4) G. H. Christie and R. C. Menzies, *ibid.*, 127, 2369 (1925).
(5) C. M. Fear and R. C. Menzies, *ibid.*, 129, 937 (1926).