

virtually quantitative yield. Representative examples are given in Table III.

Table III

RCO <sub>2</sub> Tl + R'COCl → RCOOCOR' + TlCl		Temp, °C	Time, hr <sup>a</sup>	Yield, % <sup>b</sup>
R	R'			
C <sub>6</sub> H <sub>5</sub>	CH <sub>3</sub>	5	0.25	95
C <sub>6</sub> H <sub>5</sub>	(CH <sub>3</sub> ) <sub>2</sub> CH	25	6	100
C <sub>6</sub> H <sub>5</sub>	(CH <sub>3</sub> ) <sub>3</sub> C	25	8	99
C <sub>6</sub> H <sub>5</sub>	C <sub>6</sub> H <sub>5</sub>	35	4	100
(CH <sub>3</sub> ) <sub>3</sub> C	CH <sub>3</sub>	5	0.25	97
(CH <sub>3</sub> ) <sub>3</sub> C	(CH <sub>3</sub> ) <sub>2</sub> CH	25	1	98
(CH <sub>3</sub> ) <sub>3</sub> C	(CH <sub>3</sub> ) <sub>3</sub> C	25	1	100
(CH <sub>3</sub> ) <sub>2</sub> CH	CH <sub>3</sub>	5	0.25	96
(CH <sub>3</sub> ) <sub>2</sub> CH	(CH <sub>3</sub> ) <sub>2</sub> CH	25	1	99
(CH <sub>3</sub> ) <sub>2</sub> CH	(CH <sub>3</sub> ) <sub>3</sub> C	25	1	98
H	CH <sub>3</sub>	5 <sup>c</sup>	3	67 <sup>d</sup>

<sup>a</sup> Completion of the reaction was established by examination of the ir spectra of aliquots removed from the reaction mixture at suitable intervals and observation of the disappearance of bands characteristic of the acyl or aroyl halide employed. <sup>b</sup> Spectral examination (ir, nmr) of the mixed anhydrides revealed the presence of traces (1–3%) of the corresponding symmetrical anhydrides. <sup>c</sup> Reaction allowed to warm up gradually to 25°. <sup>d</sup> Recovery was 77%. The product must be distilled to remove disproportionation products. Extended reaction times gave lower yields.

Although symmetrical anhydrides can be prepared by the above procedure, a much more convenient synthesis which does not require the intermediacy of the acid chloride is the reaction of the thallium(I) carboxylate with thionyl chloride in ether at room temperature.<sup>6</sup> The intermediate diacyl or diaroyl sulfite spontaneously loses sulfur dioxide; evaporation of the ether gives the anhydride in 96–98% yield after distillation. Representative examples are given in Table IV.

Table IV

2RO <sub>2</sub> Tl + SOCl <sub>2</sub> → (RCO) <sub>2</sub> O + SO <sub>2</sub> + 2TlCl	
R	Yield, %
CH <sub>3</sub>	98
(CH <sub>3</sub> ) <sub>2</sub> CH	97
(CH <sub>3</sub> ) <sub>3</sub> C	96
C <sub>6</sub> H <sub>5</sub>	97

The conventional synthetic procedures for anhydride formation,<sup>7,8</sup> even those utilizing other metal carboxylate salts, are not generally suitable for the preparation of mixed anhydrides because of the ease with which the latter may disproportionate above room temperature<sup>9</sup> either during the conditions of their formation or in the course of purification. The present method, which employs stoichiometric amounts of both reactants and proceeds quantitatively at room temperature or below, appears to utilize the minimal conditions requisite for mixed anhydride formation and preservation. Disproportionation can be observed even with the present

(6) This procedure is analogous to but much superior to the use of silver carboxylates; see W. S. Denham and H. Woodhouse, *ibid.*, 103, 1861 (1913).

(7) M. F. Ansell and R. H. Gigg in "Rodd's Chemistry of Carbon Compounds," S. Coffey, Ed., Elsevier Publishing Co., New York, N. Y., 1965, p 156.

(8) R. B. Wagner and H. D. Zook, "Synthetic Organic Chemistry," John Wiley and Sons, Inc., New York, N. Y., 1953, p 558.

(9) C. D. Hurd and M. F. Dull, *J. Am. Chem. Soc.*, 54, 3427 (1932).

method, however, if the mixed anhydride formed is more reactive than the acid chloride. It is therefore important to employ as reactant the carboxylate salt of the weaker acid.

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### Thallium in Organic Synthesis. III. Coupling of Aryl and Alkyl Grignard Reagents<sup>1</sup>

Sir:

Biaryls are customarily prepared from aryl halides either by the classical Ullmann reaction<sup>2</sup> or by coupling of aryl Grignard reagents with halides of such metals as Co, Cu, Hg, Ni, Ag, Au, etc.<sup>3</sup> Unless activating substituents such as a nitro group are present in the nucleus, the Ullmann reaction requires the use of the relatively expensive aryl iodide, but is of special value in the coupling of *ortho*-substituted halides. Previously described procedures for the coupling of Grignard reagents lead to mixtures of products, and the reactions are difficult to control.

We wish to report a simple, general procedure for the coupling of aryl- and *sec*-alkylmagnesium bromides using thallium(I) bromide.<sup>4</sup> The experimental procedure is illustrated by the conversion of 4-bromotoluene to 4,4'-dimethylbiphenyl.

A mixture of 0.135 mole of thallium(I) bromide and 0.0675 mole of 4-tolylmagnesium bromide in 40 ml of tetrahydrofuran–benzene (1:1) was stirred and refluxed under nitrogen for 4 hr, cooled, acidified with dilute hydrochloric acid, and filtered. The filtrate was concentrated and passed through a short column of alumina and the crude product, obtained by further concentration, recrystallized from benzene to give 4,4'-dimethylbiphenyl, mp 121°, in 91% yield.

Typical conversions are given in Table I.

As can be seen from Table I, secondary alkyl Grignard reagents give coupled products in moderate yields. On the other hand, primary aliphatic Grignard reagents give only traces of coupled alkanes; the major products of the reaction are the corresponding dialkylthallium(III) bromides. This reaction represents the method of choice for the preparation of these previously difficultly accessible compounds and will be described elsewhere.<sup>5</sup> Similarly, *ortho*-substituted aryl Grignard reagents fail to give coupled products under the above conditions; mesitylmagnesium bromide, for example, gives only dimesitylthallium(III) bromide. The anomalous course taken by this class of Grignard reagent has not yet been

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

(2) (a) P. E. Fanta, *Chem. Rev.*, 38, 139 (1946); (b) P. E. Fanta, *ibid.*, 64, 613 (1964).

(3) M. S. Kharasch and O. Reinmuth, "Grignard Reactions of Non-Metallic Substances," Constable and Co., Ltd., London, 1954, Chapter 5.

(4) Optimum conditions require 1.5–2.0 moles of thallium(I) bromide per mole of Grignard reagent.

(5) A. McKillop, L. F. Elsom, and E. C. Taylor, to be submitted for publication.

Table I

Halide	Product	Yield, % <sup>a</sup>
Bromobenzene	Biphenyl	85
4-Bromoanisole	4,4'-Dimethoxybiphenyl	99
4-Bromotoluene	4,4'-Dimethylbiphenyl	91
3-Bromotoluene	3,3'-Dimethylbiphenyl	85
4-Bromo- <i>o</i> -xylene	3,3',4,4'-Tetramethylbiphenyl	76
2-Bromo-6-methoxy-naphthalene	6,6'-Dimethoxy-2,2'-binaphthyl	73
4-Bromobiphenyl	4,4'-Quaterphenyl	91
4-Bromochlorobenzene	4,4'-Dichlorobiphenyl	73 <sup>b</sup>
4-Fluorobromobenzene	4,4'-Difluorobiphenyl	73 <sup>c</sup>
2-Bromonaphthalene	2,2'-Binaphthyl	84
Cyclohexyl bromide	Bicyclohexyl	58
Cyclopentyl bromide	Bicyclopentyl	56
2-Bromopentane	3,4-Dimethyloctane	50

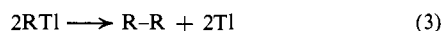
<sup>a</sup> Calculated on pure recrystallized or redistilled material.

<sup>b</sup> Accompanied by 5% di(4-chlorophenyl)thallium(III) bromide.

<sup>c</sup> Accompanied by 7% di(4-fluorophenyl)thallium(III) bromide.

fully investigated, however, and will be reported independently.

The above results are accommodated by the tentative reaction course of eq 1-6.



Equation 3 was suggested by Gilman and Jones<sup>6</sup> as the source of the small amount of biphenyl obtained on treatment of phenyllithium with thallium(I) chloride. The major product in this reaction was triphenylthallium, which we have not observed under our conditions. Contrary to the suggestion of Gilman and Jones,<sup>6</sup> we have shown that triphenylthallium does *not* disproportionate to biphenyl and thallium. The disproportionation of alkylthallium(III) dibromides (eq 4) has been observed previously in the reaction of alkyl Grignard reagents with thallium(III) bromide.<sup>7,8</sup> Arylthallium(III) dibromides, on the other hand, are known to be considerably more stable, although they do disproportionate on heating (eq 5).<sup>9</sup>

(6) H. Gilman and R. G. Jones, *J. Am. Chem. Soc.*, **68**, 517 (1946).

(7) C. R. Hart and C. K. Ingold, *J. Chem. Soc.*, 4372 (1964).

(8) D. Sarrach, *Z. Anorg. Allgem. Chem.*, **319**, 16 (1962).

(9) A. N. Nesmeyanov and R. A. Sokolik, "Methods of Elemento-Organic Chemistry. Vol. I. The Organic Compounds of Boron, Aluminum, Gallium, Indium and Thallium," The World Publishing Co., New York, N. Y., 1967.

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## An Unequivocal Synthesis of 6-Substituted Pteridine 8-Oxides, Pteridines, and 7,8-Dihydropteridines<sup>1</sup>

Sir:

Almost all naturally occurring pteridines are 6-substituted derivatives and are unsubstituted at position 7.<sup>2</sup> Their unequivocal synthesis by the classical, most widely employed synthetic route to pteridines (condensation of a 4,5-diaminopyrimidine with an  $\alpha,\beta$ -dicarbonyl compound) is therefore not possible, since this method suffers from an unavoidable ambiguity when an unsymmetrical  $\alpha,\beta$ -dicarbonyl component is employed.<sup>2,3</sup> The mixture of isomers which results is not only extremely difficult to separate but is often undetectable by normal chromatographic techniques. One can, in principle, avoid this ambiguity by initially preparing a pyrazine intermediate with a known substitution pattern and subsequently closing the pyrimidine ring,<sup>4</sup> but this approach has not seen much application and has never been used for the preparation of any naturally occurring pteridines because of inaccessibility of the requisite pyrazine intermediates.

We describe in this communication a general, unequivocal synthesis of 6-substituted pteridine 8-oxides. These compounds are readily reduced to 7,8-dihydropteridines, again of unequivocal structure; subsequent mild oxidation gives 6-substituted pteridines. The procedure readily permits wide variations in substitution patterns in both the pyrimidine and pyrazine rings and appears directly applicable to the unambiguous synthesis of a variety of naturally occurring pteridines carrying different types of substituents at C<sub>6</sub>.

Condensation of ethyl  $\alpha$ -aminocynoacetate<sup>5</sup> (**1**, R = COOC<sub>2</sub>H<sub>5</sub>) with isonitrosoacetone<sup>6</sup> (**2**, R' = CH<sub>3</sub>) in glacial acetic acid at room temperature gave 2-amino-3-carbomethoxy-5-methylpyrazine 1-oxide<sup>7</sup> (**3**, R = COOC<sub>2</sub>H<sub>5</sub>; R' = CH<sub>3</sub>, 60%; mp 134.8°) which upon reaction with guanidine in methanol containing sodium methoxide, followed by cyclization of the pyrazinoyl-guanidine intermediate by heating in DMF, gave 6-methylpterin 8-oxide (**4**, R = CH<sub>3</sub>, 65%). Both the 6-methyl and the 8-oxide groupings are positioned unambiguously by this sequence of condensation reactions.<sup>8</sup> Reduction of **4** (R = CH<sub>3</sub>) with sodium di-

(1) This work was supported by a grant (CA-02551) to Princeton University from the National Cancer Institute, National Institutes of Health, Public Health Service.

(2) For general references on pteridine chemistry, see (a) "Pteridine Chemistry," W. Pfeleiderer and E. C. Taylor, Ed., Pergamon Press, Ltd., London, 1964; (b) R. C. Elderfield and A. C. Mehta, "Heterocyclic Compounds," Vol. 9, R. C. Elderfield, Ed., John Wiley and Sons, Inc., New York, N. Y., 1967, pp 1-117; and references cited therein.

(3) See, for example (a) R. G. W. Spickett and G. M. Timmis, *J. Chem. Soc.*, 2887 (1954); (b) R. Tschesche and G. Sturm, *Chem. Ber.*, **98**, 851 (1965).

(4) For examples of this route to pteridines, see (a) S. Gabriel and A. Sonn, *ibid.*, **40**, 4850 (1907); (b) A. Albert, D. J. Brown, and G. W. H. Cheeseman, *J. Chem. Soc.*, 474 (1951); (c) E. C. Taylor, J. A. Carbon, and D. R. Hoff, *J. Am. Chem. Soc.*, **75**, 1904 (1953); (d) E. C. Taylor, R. B. Garland, and C. F. Howell, *ibid.*, **78**, 210 (1956); (e) G. P. G. Dick and H. C. S. Wood, *J. Chem. Soc.*, 1379 (1955); (f) E. C. Taylor and W. W. Paudler, *Chem. Ind. (London)*, 1061 (1955); (g) W. B. Wright and J. M. Smith, *J. Am. Chem. Soc.*, **77**, 3927 (1955).

(5) (a) A. H. Cook, I. Heilbron, and A. L. Levy, *J. Chem. Soc.*, 1594 (1947); (b) B. Ohta, *J. Pharm. Soc. Japan*, **68**, 226 (1948); *Chem. Abstr.*, **48**, 4440g (1954).

(6) Condensation of alkyl  $\alpha$ -aminonitriles with oximinomethyl ketones to give pyrazine 1-oxides (**3**, R = alkyl) was described by Sharp and Spring (W. Sharp and F. S. Spring, *J. Chem. Soc.*, 932 (1951)) during their early work on the synthesis of aspergillilic acid.

(7) Satisfactory microanalytical and spectral data (ir, uv, and nmr) were obtained for all new compounds reported. Compounds for which no melting points are reported did not melt below 320°.