## References and Notes

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# Communications

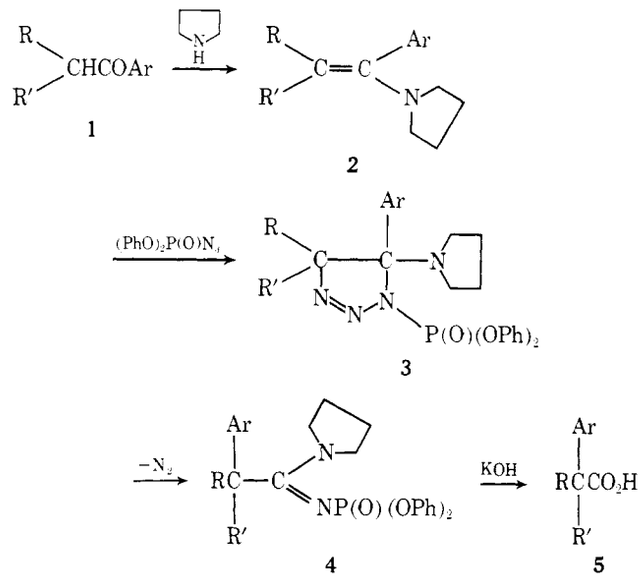
## New Methods and Reagents in Organic Synthesis. 2.[1] A Facile Conversion of Alkyl Aryl Ketones to α-Arylalkanoic Acids Using Diphenyl Phosphorazidate. Its Application to a New Synthesis of Ibuprofen and Naproxen, Nonsteroidal Antiinflammatory Agents

*Summary:* α-Arylalkanoic acids are conveniently prepared from alkyl aryl ketones by the successive treatment with pyrrolidine, diphenyl phosphorazidate (DPPA), and potassium hydroxide; the method has been efficiently applied to a new synthesis of ibuprofen and naproxen, important nonsteroidal antiinflammatory agents.

*Sir:* Recent publications from these laboratories[1,2] and others[3,4] have revealed that diphenyl phosphorazidate (DPPA, $(PhO)_2P(O)N_3$) may be used for various synthetic reactions. The 1,3-dipolar character of DPPA has been well demonstrated by its reaction with enamines of cyclic ketones, which has offered a new method of ring contraction.[2]

We now wish to report a convenient conversion of alkyl aryl ketones **1** to α-arylalkanoic acids **5** using DPPA as a 1,3-dipole in the key step. The new general method consists of three-step operations involving: (1) conversion of alkyl aryl ketones **1** to pyrrolidine enamines **2**; (2) 1,3-dipolar cycloaddition of DPPA to enamines **2** followed by aryl migration with concomitant evolution of nitrogen from labile triazoline intermediates **3**; and (3) hydrolysis of the resulting *N*-phosphorylated amidines **4**, as summarized in Scheme I.

Scheme I



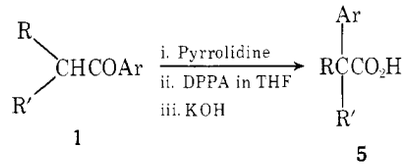

Although similar conversion of alkyl aryl ketones to esters of α-arylalkanoic acids by oxidative rearrangements utilizing thallium(III) nitrate has been reported recently,[5] the present method possesses such advantages that: (1) the functional specificity of the reactions may be much superior; (2) nonoxidative and less toxic reagents[6] can be used; and (3) all the transformations may be readily carried out in multigram quantities using a single reaction vessel.

Condensation of alkyl aryl ketones **1** with pyrrolidine smoothly proceeded in refluxing benzene or toluene in the presence of boron trifluoride etherate[7] to give enamines **2**. Addition of DPPA to enamines **2** in tetrahydrofuran (or ethyl acetate), followed by refluxing the reaction mixture, generated nitrogen to yield *N*-phosphorylated amidines **4** by aryl migration. The intermediates of this transformation are obviously 1,3-dipolar cycloadducts **3**.[2] Although optimum conditions for the reaction have yet to be established,[8] the data in Table I[9] reveal that preparatively useful yields can be obtained under relatively mild conditions.

A typical procedure is as follows. To pyrrolidine enamine **2** (R = Me; R′ = H; Ar = Ph) (3.05 g) in tetrahydrofuran (45 mL) was added with stirring DPPA (4.95 g). The mixture was stirred at room temperature for 1 h, at 40 °C for 1 h, and then refluxed for 2 h. After dilution with ethyl acetate and benzene (1:1, 150 mL), the mixture was successively washed with 5% aqueous citric acid, water, saturated aqueous sodium chloride, saturated aqueous sodium bicarbonate, water, and saturated aqueous sodium chloride. The dried solution was evaporated and the residue was purified by column chromatography on silica gel with ethyl acetate and benzene (1:5) to give the *N*-phosphorylated amidine **4** (5.68 g, 80%).

The one-flask procedure, in which the purification of the enamines by distillation was omitted,[10] as well as the use of an argon atmosphere afforded much better overall yields based on the ketones (compare entries 1 and 3). Morpholine and piperidine enamines gave lower yields (entries 4 and 5). Interestingly, neither the methyl enol ether **6**, the enol acetate **7**, nor the silyl enol ether **8** underwent the 1,3-dipolar cycloaddition reaction with DPPA.[2] Furthermore, 1-phenyl-1-propene (**9**) and ethyl 2-cyano-3-hydroxy-3-phenylacrylate (**10**) were also completely unreactive to DPPA. These results exhibit the prominent functional specificity of DPPA as a 1,3-dipole. This specific nature of the process is highlighted

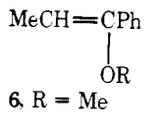
**Table I. Conversion of Alkyl Aryl Ketones 1 to α-Arylalkanoic Acids 5**



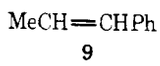

1 5

| entry | ketone 1 R | ketone 1 R′ | ketone 1 Ar | enamine 2 % yield | amidine 4 % yield | amidine 4 mp, °C | acid 5 % yield |
|---|---|---|---|---|---|---|---|
| 1 | Me | H | Ph | 79 | 80 | 74–76 | 91 |
| 2 | Me | H | Ph | | 81[a] | | |
| 3 | Me | H | Ph | *b* | 84[b,c] | | |
| 4 | Me | H | Ph | 55[d] | 63[a] | 71–73.5 | |
| 5 | Me | H | Ph | 62[e] | 67[a] | 67–69 | |
| 6 | Et | H | Ph | 77 | 74 | 83–85 | 91 |
| 7 | Et | H | Ph | | 82[c] | | |
| 8 | Et | H | Ph | *b* | 81[b,c] | | |
| 9 | Me | Me | Ph | *f* | 70[c] | 87–88.5 | quant |
| 10 | allyl | H | Ph | 79 | 80[c] | a viscous oil | 91 |
| 11 | Me | H | *g* | *b* | 71[b,c] | a viscous oil | 92 |

[a] Ethyl acetate was used as reaction solvent. [b] The one-flask procedure.[10] Yields of amidines 4 were based on ketones 1. [c] Reactions were carried out under argon. [d] Morpholine enamine. [e] Piperidine enamine. [f] Prepared according to the literature: W. A. White and H. Weingarten, *J. Org. Chem.*, **32**, 213 (1967). [g] 2-Dibenzofuranyl.




6, R = Me
7, R = MeCO
8, R = $Me_3Si$

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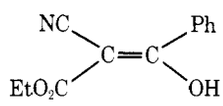


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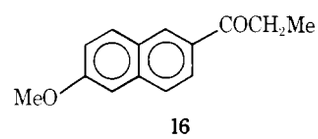
by the successful conversion of the enamine **2** (R = $CH_2$=$CHCH_2$; R′ = H; Ar = Ph) to the corresponding amidine **4** without any change of the double bond function.[11]

The reaction sequences have been completed by hydrolysis of the *N*-phosphorylated amidines **4** with potassium hydroxide in refluxing ethylene glycol to give α-arylalkanoic acids **5** in good yields.

The utility of the above conversions is demonstrated by the efficient synthesis of two important nonsteroidal antiinflammatory agents, ibuprofen (**11**) [2-(4-isobutylphenyl)-propionic acid][12] and naproxen (**12**) [2-(6-methoxy-2-naphthyl)propionic acid].[13] Thus 4-isobutylpropiophenone (**13**), prepared by the Friedel–Crafts acylation of isobutylbenzene with propionyl chloride, was converted to its pyrrolidine enamine **14**, bp 112–114 °C (0.4 mmHg), which further reacted with DPPA under argon to give the *N*-phosphorylated amidine **15**, a viscous oil, in 78% overall yield. Hydrolysis in ethylene glycol gave ibuprofen (**11**) in 79% yield.

Naproxen, though in its racemic form, was also conveniently prepared from ethyl 6-methoxynaphthyl ketone (**16**) by its condensation with pyrrolidine, forming the enamine **17**, bp 148–152 °C (0.2 mmHg), followed by the reaction with DPPA. The resulting *N*-phosphorylated amidine **18**, mp 102.5–105 °C, obtained in 82% yield, was subjected to hydrolysis as above to give naproxen (**12**) in 83% yield.

Current investigations are directed toward the application of the present method to the synthesis of many important medicinal agents bearing α-arylalkanoic acid structures.

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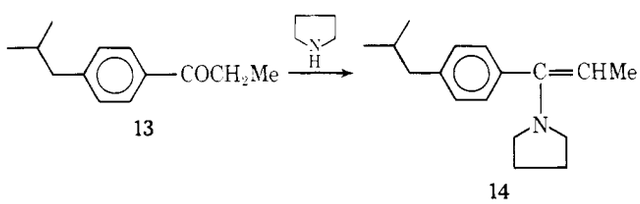


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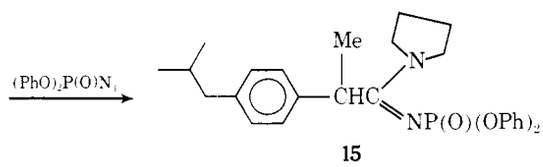


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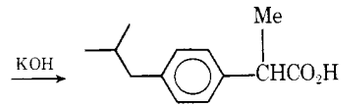


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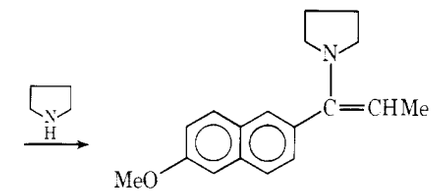


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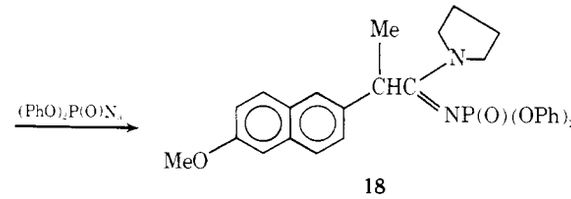


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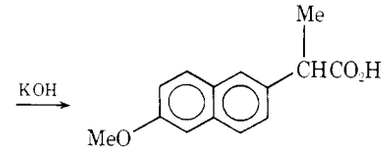


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**Acknowledgment.** We wish to thank Emeritus Professor S. Yamada and Professor K. Koga of University of Tokyo for their interests and discussions.

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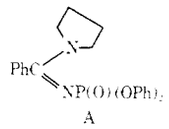
(6) DPPA itself is a stable, nonexplosive liquid: T. Shioiri, K. Ninomiya, and S. Yamada, *J. Am. Chem. Soc.*, **94**, 6203 (1972).
(7) Cf. S. Yamada, T. Oguri, and T. Shioiri, *J. Chem. Soc., Chem. Commun.*, 136 (1976); T. Oguri, T. Shioiri, and S. Yamada, *Chem. Pharm. Bull.*, **26**, 803 (1978).
(8) According to substrates and reaction conditions, 1,3-dipolar elimination products such as A from triazoline intermediates **3** were sometimes isolated, though in poor yields.



A

(9) All new compounds were fully characterized by NMR and IR spectral means and elemental composition. Known compounds were identified by comparing their physical data (melting or boiling points, IR and NMR spectra) with reported ones.
(10) In the one-flask procedure, the condensation reaction of a ketone **1** with pyrrolidine was carried out as described in the text, and the reaction solvent was removed in vacuo. Tetrahydrofuran was added to the residual crude enamine **2** under argon atmosphere, followed by the addition of DPPA. The reaction and workup were conducted as described in the typical procedure of the text.
(11) Thallium(III) nitrate is reported[5] to be quite reactive to a variety of unsaturated molecules.
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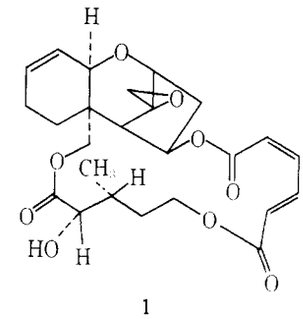
## Synthetic Strategy toward Verrucarins. An Approach toward Verrucarol

*Summary:* The synthesis of a key tetrahydrochromanone intermediate toward a sesquiterpene portion of the verrucarins, potent antitumor agents, involves novel utilization of cyclobutanone annulation, a new approach to creation of $\alpha,\beta$-unsaturated-$\gamma$-hydroxylated esters, and a new rearrangement.

*Sir:* The synthesis of the verrucarins such as verrucarin A (**1**), a class of potent antitumor agents, requires consideration of the sesquiterpene portion (cf. verrucarol, **2**) and the attendant macrocycle.[1,2] We wish to report a new approach toward verrucarol which (a) employs cyclopropyl phenyl sulfide to create most of the carbon skeleton except for the cyclohexyl ring, (b) develops a new approach to $\gamma$-hydroxylation, and (c)



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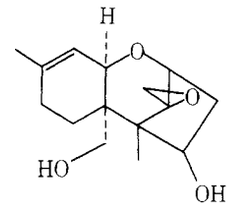

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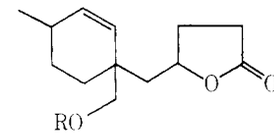


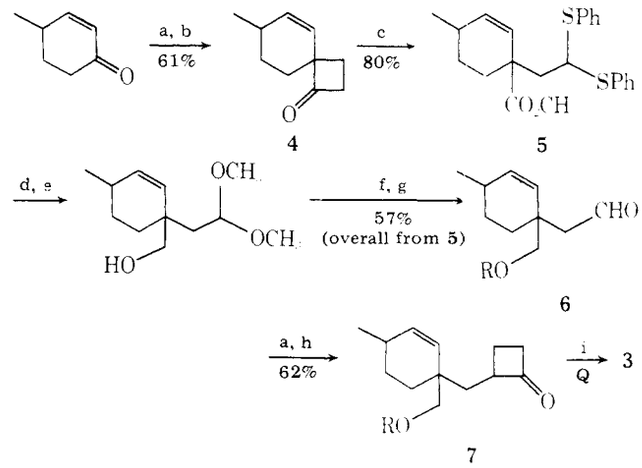
3

illustrates a novel arearrangement to create the tetrahydrochromanone ring system.

Scheme I outlines the synthesis of the key lactone **3**, which contains all of the carbon atoms of **2** save two (methyl group and epoxide methylene). [3.5]Spiroannulation of 4-methylcyclohex-2-en-1-one utilizing 1-lithiocyclopropyl phenyl sulfide[3,4] gave the desired cyclobutanone **4**[5] as a mixture of two stereoisomeric adducts (ratio ~1:1). Since this stereochemistry is immaterial with respect to the overall synthesis, no attempt was made to separate the isomers. Secosulfenylation[6] gave the desired ring-cleaved compound **5** in which the geminal carbon was fully elaborated in a functionally differentiated way. Transacetalization, reduction, O-methylation or benzoylation, and hydrolysis prepared the substrate for the final lactone annulation. Cyclobutanone annulation to **7** (R = $CH_3$ or benzoate)[5] proceeded as before, except that *p*-toluenesulfonic acid in refluxing moist benzene effected the rearrangement of the intermediate cyclopropyl carbinol.[7] Basic hydrogen peroxide[8] completed the synthesis of **3** (R = $CH_3$ or benzoate).[5] In this case, creation of the lactone via the Baeyer–Villiger oxidation takes advantage of the chemospecificity imparted by the strain of the cyclobutyl ring.

With the completion of the main parts of the carbon skeleton, attention focused upon the adjustment of the oxidation

Scheme I. Synthesis of Lactone 3




(a) c-$CH_2CH_2C(Li)(SPh)$, THF, 0 °C. (b) $HBF_4$, $H_2O$, ether, room temp. (c) $NaOCH_3$, PhSSPh, $CH_3OH$, reflux. (d) $I_2$, $CH_3OH$, reflux. (e) $LiAlH_4$, ether, reflux. (f) NaH, DME, $CH_3I$ or PhCOCl. (g) HCl, $H_2O$, THF room temp. (h) TsOH, PhH, $H_2O$, reflux (i) NaOH, $H_2O_2$, 0 °C.