In summary, the steric bulk of primary alkoxy groups in alkoxyhydrides (1) does not appear to have a major effect on their stereoselectivities. However, bulky secondary (and tertiary) alkoxy groups provide reagents with considerable steric requirements. The reagent formed from di-*tert*-butyl ketone is a remarkably highly selective one and should prove useful in synthetic applications. The great preference for formation of the less stable isomer, *trans*-**3**, compares with that observed in the kinetically controlled reduction of **2** with triisobutylaluminum.[14]

Experimental Section

Isopropyl alcohol, *sec*-butyl alcohol, isobutyl alcohol, and cyclopentanol were chromatoquality reagents purchased from Matheson Coleman and Bell. The other addends were commercially obtained and their purities were checked by glc. Gas–liquid partition chromatography was carried out with a Hewlett-Packard 5750 gas chromatograph. For the analyses of the reduction product, a 10-ft 10% Carbowax 20M acid washed and silanized column was used at 145°.

Reaction of $LiAlH_4$ with 3,3-Dimethyl-2-butanol. Reduction of Dihydroisophorone (2).—The procedure for this reaction is typical of that used in all the reductions. Standardized lithium aluminum hydride in ether (40 ml, 0.28 *M*, 0.011 mol of $LiAlH_4$) was added by pipet to a 250-ml reactor equipped with a magnetic stirrer, equilibrated addition funnel, and condenser. A solution of the alcohol (3.373 g, 0.033 mol) in 15 ml of diethyl ether was added dropwise, with stirring. After stirring for 20 min, a solution of **2**[10] (1.54 g, 0.011 mol) in 10 ml of ether was added dropwise. After 30 min, the cooled reaction mixture was hydrolyzed with water, followed by 10% sulfuric acid. The aqueous portion was extracted with ether and the combined ether solution was washed with saturated sodium bicarbonate and salt solution and dried over anhydrous $MgSO_4$. The solution was concentrated by distillation through a 18-in. helix packed fractionating column (oil bath temperature to 63°). The concentrated solution was directly analyzed by glc showing 77% of the *trans* (axial)-**3** and 23% of *cis*-**3**. Unreacted **2** represented 9% of the three components.

Registry No.—**1** (R = H), 16853-85-3; **1** (R = Me), 12076-93-6; **1** (R = Et), 17250-30-5; **1** (R = *i*-Bu), 38884-26-3; **1** [R = $(CH_3)_3CCH_2$], 38884-27-4; **1** (R = *i*-Pr), 38960-86-0; **1** (R = *sec*-Bu), 38884-28-5; **1** [R = $(CH_3)_2CHCHCH_3$], 38884-29-6; **1** [R = $(CH_3)_3$-$CCHCH_3$], 38884-30-9; **1** (R = *t*-BuCHBu-*t*), 38884-31-0; **1** (R = cyclohexyl), 38884-32-1; **1** (R = cyclopentyl), 38884-33-2; **2**, 873-94-9; *cis*-**3**, 933-48-2; *trans*-**3**, 767-54-4; 3,3-dimethyl-2-butanol, 464-07-3.

(14) H. Haubenstock and E. B. Davidson, *J. Org. Chem.*, **28**, 2772 (1963).

Base-Induced Cyclizations of Diethyl 4-Oxa-6-heptyne-1,1-dicarboxylate[1]

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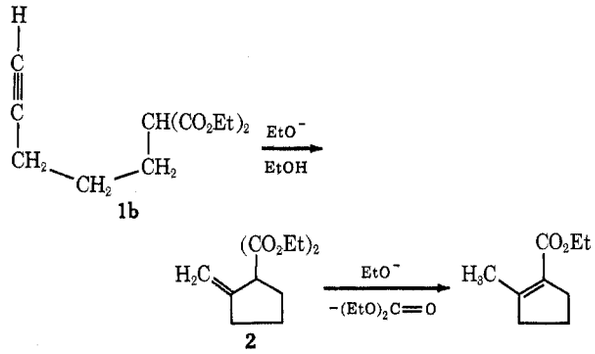
As a continuation of efforts[2] directed toward determining the scope and limitations of reactions with base of compounds that can be represented generally by **1**, we prepared diethyl 4-oxa-6-heptyne-1,1-di-

$$HC{\equiv}CCH_2Y(CH_2)_nZH$$
1

carboxylate [**1a**, Y = O, Z = $C(CO_2Et)_2$, n = 2] and studied its reaction with sodium ethoxide in ethanol and potassium *tert*-butoxide in dimethyl sulfoxide.

Eglinton and Whiting[3] reported that it was possible to isolate 1,1-dicarboethoxy-2-methylenecyclopentane (**2**) from the reaction of diethyl malonate, sodium ethoxide, and 4-pentynyl *p*-toluenesulfonate in refluxing ethanol, and they showed that the product arose by cyclization of the intermediate diethyl 5-hexyne-1,1-dicarboxylate [**1b**, Y = CH_2, Z = $C(CO_2Et)_2$, n = 1].[4] They observed that, when more than 1 equiv of sodium ethoxide was used, decarboethoxylation of the cyclic diester and migration of the double bond took place.



Significantly, Eglinton and Whiting[3] found that diethyl 6-heptyne-1,1-dicarboxylate [**1**, Y = CH_2, Z = $C(CO_2Et)_2$, n = 2] would not cyclize under conditions which converted **1b** to **2**.

1a was prepared conveniently by alkylation of diethyl malonate with 6-bromo-4-oxa-1-hexyne.[5] Treatment of **1a** with a slight excess of sodium ethoxide in boiling ethanol for 8 hr gave a 78% conversion to a 1:1.4 mixture of 4-carboethoxy-5,6-dihydro-3-methyl-1,4-oxin (**3**) and 4-carboethoxy-2,3,6,7-tetrahydrooxepin (**4**), which could be separated by fractional distillation. In a separate experiment a 74% yield of diethyl carbonate was also obtained. Structures were assigned to **3** and **4** on the basis of their spectroscopic properties and analytical data.

By analogy with the behavior of propargyloxyethanols (**1**, Y = Z = O, n = 2) when treated with base in hydroxylic solvents,[2a] the first step in formation of **3** and **4** can be pictured as intramolecular nucleophilic addition of substituted malonate anion to the internal and terminal acetylenic carbons to give the diesters **3a** and **4a**.[6] In the presence of excess base, this is followed by decarboethoxylation of the diesters with formation of diethyl carbonate and migration of the double bonds. It seems likely that decarboethoxylation

(1) Supported in part by Grant CA-10740 from the U. S. Public Health Service.

(2) (a) A. T. Bottini and J. G. Maroski, *J. Org. Chem.*, **38**, 1455 (1973); (b) A. T. Bottini and E. F. Böttner, *ibid.*, **31**, 586 (1966), and references cited therein.

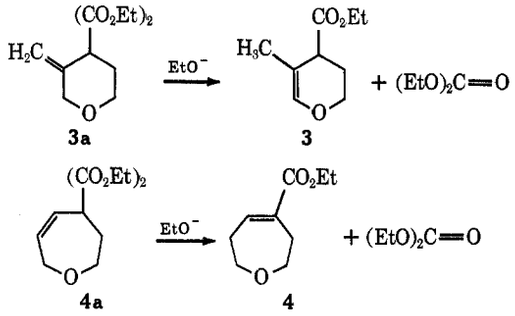
(3) G. Eglinton and M. C. Whiting, *J. Chem. Soc.*, 3052 (1953).

(4) Similar cyclizations of *cis*-hex-5-yn-3-ene-1,1-dicarboxylates to 1,1-dicarboethoxy-2-methylene-3-cyclopentenes have been reported. See M. V. Mavrov and V. F. Kucherov, *Izv. Akad. Nauk SSSR, Ser. Khim.*, 1559 (1967), and references cited therein.

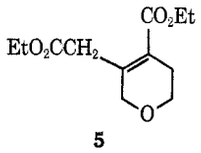
(5) D. Black, S. Landor, A. Patel, and P. Whiter, *J. Chem. Soc. C*, 2260 (1967).

(6) The faster rate of cyclization of **1a** relative to diethyl 6-heptyne-1,1-dicarboxylate[3] on treatment with sodium ethoxide in ethanol is most likely due to the electron-withdrawing effect of oxygen, which makes the acetylenic carbons more susceptible to nucleophilic attack.

of **3a** first gives the α,β-unsaturated ester, which is then converted to more stable **3**.



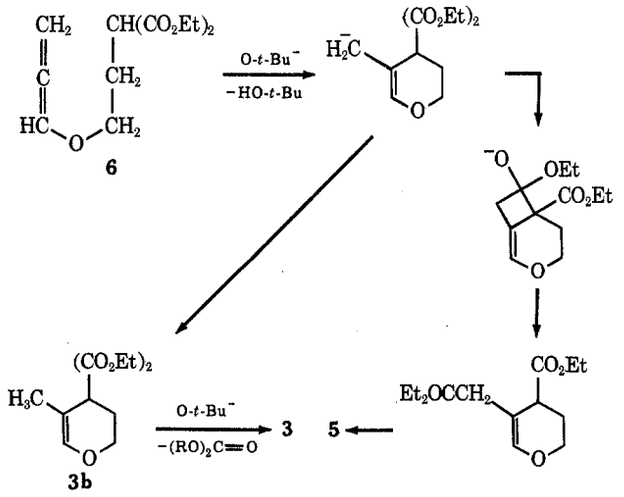
The reaction of **1a** with potassium *tert*-butoxide in dimethyl sulfoxide was also investigated. This reaction gave a relatively poor yield (<20%) of a complex mixture of six cyclic products, and the major products were identified as **3**, 4-carboethoxy-5,6-dihydro-3-ethoxycarbonylmethyl-1,2-oxin (**5**), and the *tert*-butyl homolog



of **3**. The last product was identified solely on the basis of its nmr spectrum.

The absence of the seven-membered ring product **4** from the product mixture indicated that **3** may have been formed in dimethyl sulfoxide by a pathway that did not involve direct cyclization of **1a**. Again by analogy with the behavior of propargyloxyethanols under comparable reaction conditions,[2a] an alternative mechanism leading to **3** can be pictured. In this mechanism, **1a** first undergoes prototropic rearrangement to give diethyl 4-oxa-5,6-heptadiene-1,1-dicarboxylate (**6**), which cyclizes by intramolecular nucleophilic addition of malonate to the central allene carbon to give the diester **3b**; decarboethoxylation of **3b** then gives **3**.

Intermediacy of the allene **6** also yrovides a reasonable explanation for the novel trans carboethoxylation leading to **5**. In addition to undergoing protonation to give **3b**, the cyclic carbanionic intermediate can also



give **5** *via* a bicyclic intermediate formed by addition of the carbanion to carbonyl carbon.

In addition to **1a**, several related compounds (**1**, Y = O, Z = $CHCO_2H$, n = 2; **1**, Y = O, Z = CHCO-CH_3, n = 2; **1**, Y = O, Z = CO_2^-, n = 2) were prepared and their reactions with base were investigated. None of the reactions gave a cyclic product formed by intramolecular nucleophilic addition to unsaturated carbon.[7]

Experimental Section

Temperatures are uncorrected. Ir spectra were obtained with a Beckman IR-8 spectrophotometer. Uv spectra were recorded using a Beckman DB spectrophotometer for solutions prepared from 95% EtOH. Mass spectra were obtained with a Consolidated Electrodynamics Corp. type 21-104 mass spectrometer; an ionizing voltage of 70 eV was used. Nmr spectra were obtained of CCl_4 solutions with a Varian Associates A-60A spectrometer; resonance frequencies were determined relative to 1–2% internal TMS. Vpc chromatograms were obtained with an Aerograph Model A-700 or A-90. Microanalyses were performed at Galbraith Laboratories, Inc., Knoxville, Tenn. Potassium *tert*-butoxide (KO-*t*-Bu) was obtained from MSA Research Corp.

Diethyl 4-Oxa-6-heptyne-1,1-dicarboxylate (1a).—To a stirred solution of 30.6 g (0.19 mol) of 6-bromo-4-oxa-1-hexyne,[5] 161 g (1.0 mol) of diethyl malonate, and 50 ml of PhH was added 4.13 g (0.17 mol) of PhH-washed sodium hydride at 35° in 3 hr. During the addition NaBr precipitated. When the addition was complete, the mixture was heated at 50–55° for 41 hr. The mixture was cooled and filtered, and the filtrate was washed with saturated NaCl (150 ml) and dried ($MgSO_4$). Distillation gave 19.9 g (49%) of the diester: bp 94–96° (0.1 mm); n^{23}D 1.4425; nmr δ 4.21 (q, 4, J = 7.4 Hz, $CO_2CH_2CH_3$), 4.12 (d, 2, J = 2.4 Hz, $OCH_2C{\equiv}C$), 3.58 (t, 2, J = 6.0 Hz, OCH_2CH_2), 3.49 (t, 1, J = 7.2 Hz, CH_2CH), 2.43 (t, 1, J = 2.4 Hz, $\equiv CH$), 2.32–2.05 (m, 2, J = 6.0 and 7.2 Hz, OCH_2CH_2CH), and 1.34 ppm (t, 6, J = 7.4 Hz, OCH_2CH_3).

Anal. Calcd for $C_{12}H_{18}O_5$: C, 59.52; H, 7.43. Found: C, 59.25; H, 7.41.

Reactions of Diethyl 4-Oxa-6-heptyne-1,1-dicarboxylate (1a). A. With Sodium Ethoxide in Ethanol.—To 4.73 g (19.5 mmol) of **1a** was added 15 ml of 1.3 *M* NaOEt in EtOH. The mixture was stirred and heated under reflux for 8 hr. During this time, 20-μl aliquots were taken and analyzed by vpc (SE-30). The reaction mixture was cooled and neutralized with glacial acetic acid, and the resulting mixture was added to 30 ml of ice water and extracted with ether (3 × 30 ml). The ether solutions were combined, washed with saturated NaCl (15 ml), and dried ($MgSO_4$). Analysis by vpc before distillation indicated the presence of 4-carboethoxy-5,6-dihydro-3-methyl-1,4-oxin (**3**) and 4-carboethoxy-2,3,6,7-tetrahydrooxepin (**4**) in a ratio of 1:1.4. Also present were diethyl carbonate, **1a**, and a product with retention time near that of **1a**, which was identified tentatively as diethyl 4-oxa-5,6-heptadiene-1,1-dicarboxylate (**6**). Distillation gave a fraction with bp 46–56° (30 mm) and 45–91° (0.1 mm), which contained 0.70 g (21%) of the dihydrooxin, 1.00 g (30%) of the tetrahydrooxepin, 0.32 g of **1a** and **6**, and 1.70 g (74%) of diethyl carbonate. The components of the mixture were isolated by preparative vpc, and diethyl carbonate and **1a** were identified by comparison with known samples.

3 had $n^{23.5}$D 1.4561; ir 1730 (vs, C=O), 1665 cm^{-1} (s, C=C); nmr δ 6.19 (q, 1, J = 1 Hz, OCH=), 4.45–3.81 (m, 4, OCH_2CH_3 and OCH_2CH_2CH), 2.80 (t, 1, J = 5 Hz, CH_2CHCO_2), 2.30–1.74 (m, 2, OCH_2CH_2CH), 1.59 (d, 3, J = 1 Hz, $CH{=}CCH_3$), and 1.25 ppm (t, 3, J = 7.5 Hz, OCH_2CH_3); mass spectrum m/e (rel intensity) 170 (12), 97 (100), 69 (10).

Anal. Calcd for $C_9H_{14}O_3$: C, 63.55; H, 8.23. Found: C, 63.89; H, 7.93.

4 had n^{24}D 1.4742; uv λ_{max} 223 mμ (ϵ 6440); ir 1710 (vs, C=O) and 1645 cm^{-1} (m, C=C); nmr δ 7.08 (t, 1, J = 6.0 Hz, C=CH), 4.12 (q, 2, J = 7.2 Hz, OCH_2CH_3), 3.68–3.52 (m, 4, $CH_2CH_2OCH_2CH_3$), 2.78–2.31 (m, 4, $CH_2CH_2OCH_2CH_3$), and 1.28 ppm (t, 3, J = 7.2 Hz, OCH_2CH_3); mass spectrum m/e (rel intensity) 170 (13), 140 (81), 125 (31), 112 (99), 111 (12), 97 (22), 96 (10), 95 (12), 94 (20), 83 (10), 68 (14), 67 (100), 66 (47), 65 (23).

Anal. Calcd for $C_9H_{14}O_3$: C, 63.55; H, 8.23. Found: C, 63.46; H, 8.37.

6 had ir 1950 (C=C=C) and 1730 cm^{-1} (C=O); nmr δ 6.61 (t, J = 6.0 Hz, OCH=C=C), 5.37 (d, J = 6.0 Hz, OCH=C=CH_2), 4.12 (q, J = 7.2 Hz, OCH_2CH_3), 3.54 (t, J = 6.0 Hz,

(7) These reactions are described in the Ph.D. Thesis of J. G. Maroski, University of California, Davis, 1971.

CH_2CH_2O), 3.40 [t, J = 7.0 Hz, $CH(CO_2)_2$], 2.41–1.98 (m, OCH_2CH_2CH), and 1.25 ppm (t, J = 7.2 Hz, OCH_2CH_3). A satisfactory analysis of **6** was not obtained.

A larger scale reaction was carried out for 8 hr. From 28.9 g (0.12 mol) of **1a**, NaOEt prepared from 3.0 g (0.13 g-atom) of sodium, and 130 ml of EtOH was obtained 4.86 g (24%) of **3**, bp 105–106° (19 mm), $n^{24}D$ 1.4562, 3.55 g (18%) of **4**, bp 108–110° (11 mm), $n^{24}D$ 1.4742, 3.91 g of intermediate fractions containing varying amounts of **3** and **4**, and 6.10 g of residue, which contained 1.95 g of **4**, 0.85 g of **6**, and 2.68 g of **1a**. The conversion of **1a** to **3** and **4** was 78%.

B. With Potassium *tert*-Butoxide in Dimethyl Sulfoxide.—A mixture prepared from 11 ml of dry DMSO, 2.35 g (21 mmol) of KO-*t*-Bu, and 5.1 g (21 mmol) of **1a** was heated at 100° for 4 hr and then worked up as described for the reaction with NaOEt in EtOH. Vpc analysis of the ether solution indicated the presence of diethyl carbonate, **3**, **6**, compounds subsequently identified as the *tert*-butyl homolog of **3** and 4-carboethoxy-5,6-dihydro-3-ethoxycarbonylmethyl-1,2-oxin (**5**), and at least three other products which had retention times similar to those of the cyclic products and which were not identified. Distillation gave a 1.2-g fraction, bp 50–65° (0.4 mm), which was estimated by vpc to contain 0.36 g (10%) of **3**, 0.06 g (1.5%) of the *tert*-butyl homolog of **3**, 0.14 g (2.8%) of **5**, and 0.18 g (3.5%) of **6**. These products were isolated by preparative vpc, and **3** and **6** were identified by comparison with previously identified material.

4-Carbo-*tert*-butoxy-5,6-dihydro-3-methyl-1,4-oxin had nmr δ 6.16 (q, J = 1 Hz, OCH=C), 1.61 (d, J = 1 Hz, $OCH=CCH_3$), and 1.43 ppm [s, $C(CH_3)_3$].

5 had $n^{23}D$ 1.4705; uv λ_{max} 223 mμ (ε 7380); ir 1735 (vs, unconjugated C=O), 1710 (conjugated C=O), 1655 cm^{-1} (conjugated C=C); nmr δ 4.12 (q, J = 7.0 Hz, $C=CCO_2CH_2CH_3$), 4.08 (q, J = 7.0 Hz, $CH_2CO_2CH_2CH_3$), 4.05–4.00 (m, $OCH_2C=$), 3.69 (t, J = 5.5 Hz, OCH_2CH_2CH), 3.29 (s, $=CCH_2CO_2$), 2.54–2.20 (m, $OCH_2CH_2C=$), 1.26 (t, J = 7.0 Hz, $=CCO_2CH_2CH_3$), 1.23 (t, J = 7.0 Hz, $CH_2CO_2CH_2CH_3$); mass spectrum m/e (rel intensity) 197 (29), 196 (78), 169 (34), 168 (45), 140 (62), 111 (25), 29 (100).

Anal. Calcd for $C_{12}H_{18}O_5$: C, 59.52; H, 7.43. Found: C, 59.36; H, 7.57.

The reaction was repeated using 2.17 g (19.4 mmol) of KO-*t*-Bu and 4.80 g (19.8 mmol) of **1a** except that heating at 100° was maintained for 1 rather than 4 hr. Work-up gave a 2.1-g fraction with bp 45–124° (0.2 mm), which was estimated by vpc to contain 0.20 g (6%) of **3**, 0.08 g (2.1%) of the *tert*-butyl homolog of **3**, 0.47 g (10%) of **5**, and 0.87 g (18%) of **6**.

Registry No.—**1a**, 38858-63-8; **3**, 38858-64-9; **3** *tert*-butyl homolog, 38858-65-0; **4**, 38858-66-1; **5**, 38858-67-2; **6**, 38858-68-3; 6-bromo-4-oxa-1-hexyne, 18668-74-1; diethyl malonate, 105-53-3; sodium ethoxide, 141-52-6; potassium *tert*-butoxide, 865-47-4.

Acknowledgments.—Availability of the mass spectrometer was made possible by a grant from the National Science Foundation. We wish to thank Mr. J. Voth for determination of the mass spectra.

o-Dibenzoyl Heterocycles *via* Cycloaddition Reactions. A Convenient Route to Fused Pyridazine Systems[1]

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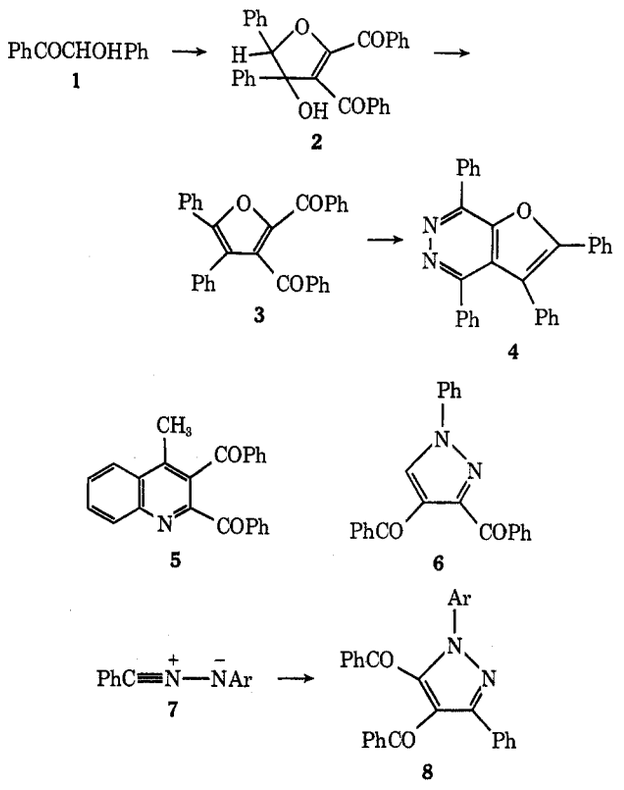
Received November 9, 1972

The synthesis of pyridazines from 1,4 diketones and hydrazine hydrate is well-established procedure,[2] its major limitation being the availability of the required 1,4-dicarbonyl precursors. These are especially difficult to obtain in heterocyclic ring systems and this study was undertaken to evaluate cycloaddition procedures as routes to heterocycles with the requisite vicinal dicarbonyl substituents, as well as the final ring closure to the fused pyridazine derivatives themselves.

Utilizing Michael additions[3] as well as a variety of 1,3-dipolar cycloadditions[4] with the acetylenic dipolarophile dibenzoylacetylene, it has been possible to obtain several heterocyclic systems with the requisite substitution pattern. The following reactions illustrate a procedure which should be capable of extension to the synthesis of other heterocycles with analogous substitution patterns.

Condensation of benzoin (**1**) with dibenzoylacetylene in the presence of potassium carbonate gave the hydrated furan **2**, which was readily dehydrated with methanolic hydrochloric acid to 2,3-dibenzoyl-4,5-diphenylfuran (**3**). Treatment of **3** with hydrazine hydrate afforded 2,3,4,7-tetraphenylfuro[2,3-*d*]pyridazine (**4**) in 80% yield. The analytical and spectral data described in Table I and the Experimental Section for this series of products clearly establish their structures.



Similarly, condensation of *o*-aminoacetophenone with dibenzoylacetylene gave 2,3-dibenzoyl-4-methylquinoline (**5**), which was converted into 1,4-diphenyl-10-methylbenzo[*g*[pyrido[2,3-*d*]pyridazine in quantitative yield.

Two isomeric dibenzoylpyrazoles are readily synthesized by 1,3-dipolar cycloaddition techniques. We have recently shown[5] that the reaction of *N*-phenyl-

(1) Support of this work by U. S. Public Health Service Research Grant CA 08495, National Cancer Institute, is gratefully acknowledged.

(2) M. Tisler and B. Stanovnik, *Advan. Heterocycl. Chem.*, **9**, 226 (1968).

(3) J. B. Hendrickson, R. Rees, and J. F. Templeton, *J. Amer. Chem. Soc.*, **86**, 107 (1964).

(4) *E.g.*, see R. Huisgen, H. Gotthardt, and R. Grashey, *Chem. Ber.*, **101**, 536 (1968); K. T. Potts and D. N. Roy, *Chem. Commun.*, 1061, 1062 (1968).

(5) K. T. Potts and D. McKeough, *J. Amer. Chem. Soc.*, **94**, 6215 (1972).