and aerated at 0 °C for 4–9 h and then at 25 °C for 15–20 h. A solution of 0.2–1.4 mL of concentrated hydrochloric acid in 20–50 mL of water was added to the reaction mixture and stirring was continued for 20–30 min. The product was then isolated, by either extraction or filtration, and recrystallized.

Isatin (3a). According to the general procedure, 0.48 g of 3-methylthiooxindole in 200 mL of dry diethyl ether was aerated for 4 h at 0 °C and 20 h at 25 °C. Acidification with 0.22 mL of concentrated hydrochloric acid in 25 mL of water followed by extraction with ether, drying of the extracts over anhydrous magnesium sulfate, filtration, and evaporation of the filtrate gave an orange solid. Recrystallization from chloroform gave 0.13 g (32% yield) of pure isatin, mp 199–200 °C.

5-Carboethoxyisatin (3b). According to the general procedure, 4.06 g of **1b** in 250 mL of dry THF was stirred and aerated for 6 h at 0 °C and 18 h at 25 °C. Acidification with 1.35 mL of concentrated hydrochloric acid in 25 mL of water, followed by extraction with ether and normal workup (vide supra), gave a yellow solid which was recrystallized from ethyl acetate to yield 2.20 g (60%) of **3b,** mp 205–206 °C.

5-Methylisatin (3c). According to the general procedure, 1.58 g of **1c** in 250 mL of dry THF was stirred and aerated for 5 h at 0 °C and 19 h at 25 °C. Acidification with 0.68 mL of concentrated hydrochloric acid in 50 mL of water, followed by extraction with ethyl acetate and normal workup (vide supra), gave 1.21 g of an orange solid. Recrystallization from 95% ethanol gave 0.54 g (41% yield) of **3c,** mp 184–185 °C.

7-Methylisatin (3d). Utilizing the general procedure, 3.30 g of **1d** in 250 mL of THF was stirred and aerated for 6 h at 0 °C and 18 h at 25 °C. Acidification with 1.42 mL of concentrated hydrochloric acid in 20 mL of water, followed by addition of a saturated brine solution, gave an organic layer which was separated and worked up as described above to give 1.98 g of crude product. Recrystallization from methanol gave 1.09 g (40% yield) of **3d,** mp 268–270 °C.

5-Chloroisatin (3e). According to the general procedure, 2.10 g of **1e** in 250 mL of THF was stirred and aerated for 4 h at 0 °C and 20 h at 25 °C. Acidification with 0.8 mL of concentrated hydrochloric acid in 25 mL of water resulted in the precipitation of an orange solid (1.10 g), which was collected by filtration. Addition of a saturated sodium chloride solution to the filtrate gave an organic phase which was separated and worked up as described above to give an additional 0.57 g of orange solid. Recrystallization of the crude product from 95% ethanol gave 0.90 g (49% yield) of **3e,** mp 246–247 °C.

5-Methoxyisatin (3f). Oxidation, according to the general procedure, of 1.80 g of **1f** in 250 mL of dry THF was carried out for 6 h at 0 °C and 18 h at 25 °C. Acidification with 0.72 mL of concentrated hydrochloric acid in 25 mL of water, followed by extraction with ether and a standard workup procedure (vide supra), gave a dark red solid which was recrystallized from methanol to give 0.42 g (27% yield) of **3f,** mp 201–203 °C.

5-Cyanoisatin (3g). According to the general procedure, 0.62 g of **1g** in 200 mL of dry THF was stirred and aerated for 9 h at 0 °C and 15 h at 25 °C. Acidification with 0.25 mL of concentrated hydrochloric acid in 25 mL of water, followed by extraction with ether and standard workup (vide supra), gave an orange solid. Recrystallization from 95% ethanol gave 0.18 g (35% yield) of **3g,** mp 273–274 °C dec.

Acknowledgment. We are indebted to the National Science Foundation Undergraduate Research Participation program and to the General Electric Foundation for summer support for K.M.H.

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Simple Method for the Synthesis of Some Pyridazines

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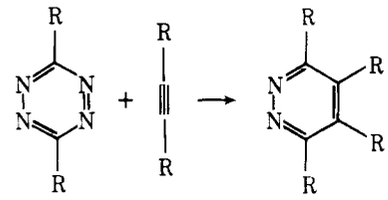
Received August 14, 1978

The reaction of olefinic and acetylenic compounds with 3,6-disubstituted-1,2,4,5-tetrazines (**1**) to give substituted pyridazines (**2**) was first reported by Carboni and Lindsey.[1]

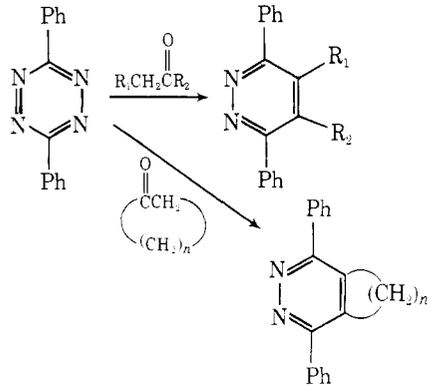


1 **2**

Analogous reactions of **1** with enol ethers, ketene acetals, enol esters, and enamines were shown by Sauer and co-workers[2a] to yield pyridazine derivatives. We report a simple one-step method for the synthesis of substituted pyridazines.

Treatment of 3,6-diphenyl-1,2,4,5-tetrazine (**1**, R = Ph) with a variety of aldehydes and ketones (Table I) in base, at room temperature, proceeded smoothly to give the corresponding pyridazines. The reaction is often immediate and accompanied by the evolution of nitrogen and the disappearance of the violet-red color of **1**. It was observed that aldehydes were more reactive than their isomeric ketones. The

Table I



R_1	R_2	n	product[g]	% yield	reaction time, min	mp, °C
H	H		**3**	88	8	220–222[a]
CH_3	H		**4**	81	3	132–134[b]
C_2H_5	H		**5**	41	2	77–79
H	$CH(OCH_3)_2$		**6**	56	4	79–81
Ph	H		**7**	74	1.5	168–170[c]
H	Ph		**7**	58	13	168–170
H	CH_3		**4**	72	5	132–134[d]
$PhCH_2$	H		**8**	51	1.5	111–113
CH_3	CH_3		**9**	52	25	208–210[e]
CH_3	C_2H_5		**10**	30	120	119–121
		3	**11**	67	1	158–159[f]
		4	**12**	58	3	171–173
		5	**13**	61	8	150–152
		6	**14**	11	12 h	138–139

[a] Lit.[1,3] mp 220–222 and 228–229 °C. [b] Lit.[3] mp 135–136 °C. [c] Lit.[1,3,4] mp 176–177 and 170 °C. [d] Neat. [e] Pyridazine **5** (10%) was isolated by TLC. [f] Lit.[3] mp 156.5–157.5 °C. [g] Satisfactory analytical data (±0.3% for C, H, and N) were provided for compounds **5, 6, 8–10,** and **12–14** (Ed.).

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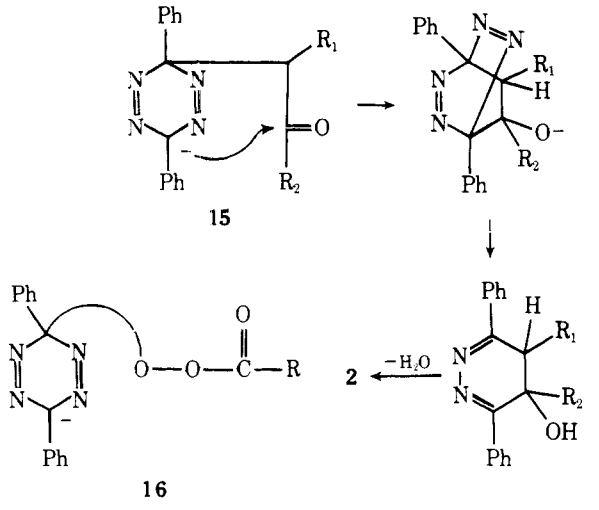
Scheme I



reactivity of the cyclic ketones increased with decreasing ring size. Moreover, cyclic ketones were more reactive than their open-chain analogues, but less reactive than aldehydes. Although we prefer a stepwise mechanism that involves intermediate **15** for the reaction of **1** with enolate anions (Scheme I), the possibility of a Diels–Alder reaction with "inverse" electron demand cannot be excluded. The latter has been advanced[2] as the mechanism through which vinyl ethers, vinyl esters, ketene acetals, ketene aminals, and enamines react with **1**.

Furthermore, we found that **1** (R = Ph) reacted instantaneously with peracids or peroxides, in base, to give 2,5-diphenyl-1,3,4-oxadiazole in good yield. The latter compound was obtained by Hancock[5] and co-workers in a reaction of **1** (R = Ph) were peracetic acid (24 h). It is likely that the remarkable enhancement of the rate of the former reaction is due to the availability of the peracid anion, which initiates the nucleophilic attack on the relatively electron-poor tetrazine to give intermediate **16**. The hydrolysis of **1** (R = Ph) with base to give benzoylbenzaldehyde hydrazone (PhCH=NNHCOPh) can be envisaged to proceed by an analogous mechanism and therefore renders the mechanism of Libman and Slack[6] untenable.

The merits of the present method become apparent when compared with some of the literature methods for the preparation of pyridazines **3, 4,** and **7,** which were obtained after heating for 50, 70 h, and 3 days, respectively.[1,3,4]

The generality of the reaction of **1** (R = Ph or 2-pyridyl) with enolate anion seems to be subject to steric effects. It was found that pinacolone and 1-adamantyl methyl ketone did not react with **1** under the conditions of the reaction. Nevertheless, the present method provides a convenient route into the preparation of a large number of substituted pyridazines, some of which are inaccessible by other methods.

Experimental Section

Melting points were determined on a Fisher-Johns melting point apparatus and are uncorrected. Infrared spectra were taken as KBr discs using Perkin-Elmer 257 or 621 grating infrared spectrophotometers. Merck silica gel $60PF_{254}$ was used in TLC. Elemental analyses were performed by F. Pascher, W. Germany.

3,6-Diphenyl-1,2,4,5-tetrazine (1, R = Ph) was prepared in 37% yield according to the literature[7] method with a slight modification where the product was leached with carbon disulfide to remove elemental sulfur.

General Procedure for the Preparation of Pyridazines 3–14. 3,6-Diphenyl-1,2,4,5-tetrazine (0.25 g, 1.1 mmol) and the appropriate aldehyde or ketone (2.2 mmol) were mixed with dry peroxide-free tetrahydrofuran (10 mL). The mixture was magnetically stirred at room temperature, and a solution (1 mL) of 2.5% methanolic potassium hydroxide was added to it. In most of the cases the reaction ensued immediately, and the termination of the reaction was indicated by the cessation of nitrogen evolution and the discharge of the violet-red color of the tetrazine. The solvent was evaporated, and the resulting residue was washed with water (40 mL), collected by suction filtration, dried, and recrystallized from the appropriate solvent, usually ethanol or methanol–water.

The strong bands of the infrared spectra of the new pyridazines are as follows. **5**: 1583, 1443, 1397, 772, 756, 694 cm^{-1}. **6**: 1449, 1398, 1106, 1058, 990, 779, 761, 715, 708 cm^{-1}. **8**: 1400, 769, 740, 706 cm^{-1}. **9**: 1380, 1020, 760, 710 cm^{-1}. **10**: 1375, 780, 707 cm^{-1}. **12**: 2915, 1375, 756, 694 cm^{-1}. **13**: 1548, 1478, 1447, 1070, 790, 720, 697 cm^{-1}. **14**: 2940, 1376, 742, 688 cm^{-1}.

Registry No.—**1** (R = Ph), 6830-78-0; **3,** 891-22-5; **4,** 2242-68-4; **5,** 3238-12-8; **6,** 68629-91-4; **7,** 2272-58-4; **8,** 68629-92-5; **9,** 23063-11-8; **10,** 68629-73-2; **11,** 2272-61-9; **12,** 68629-74-3; **13,** 68629-75-4; **14,** 68629-76-5; acetaldehyde, 75-07-0; propanal, 123-38-6; butanal, 123-72-8; 1,1-dimethoxy-2-propanone, 6342-56-9; benzeneacetaldehyde, 122-78-1; acetophenone, 98-86-2; acetone, 67-64-1; benzenepropanal, 104-53-0; 2-butanone, 78-93-3; 3-pentanone, 96-22-0; cyclopentanone, 120-92-3; cyclohexanone, 108-94-1; cycloheptanone, 502-42-1; cyclooctanone, 502-49-8.

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1-Benzoyl-2-thiobiuret: Rearrangement and Cyclization

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Received September 19, 1978

In attempting a water recrystallization of 1-benzoyl-2-thiobiuret (**1**), a yellow crystalline compound melting at 171–173 °C, we observed the formation of a white material (**2**) melting at 230–231 °C. Complete conversion of **1** to **2** could be effected by heating an aqueous suspension of the former compound for ca. 16 h. Elemental analysis and mass spectrometry established that the white compound was isomeric with **1** whereas a positive ammoniacal silver nitrate test indicated the retention of the thioureido moiety. These considerations suggested that the new isomer might be 1-benzoyl-4-thiobiuret (**2**).

The arrangement of the carbon–nitrogen skeleton of the isomer was established by conversion of **1** and **2** to their *S*-methiodide derivatives which then underwent methanolysis to yield 1-benzoylbiuret (**3**). This type of reaction has been observed to occur in activated thioureas.[1]