The Synthesis of 3-Aryl-6-alkylpyridazines

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Nine compounds of general structure R-X-Y-R′ where X is a *para*-disubstituted phenyl ring and Y is a 3,6-disubstituted-pyridazine ring were synthesized. These can be used as liquid crystal dopents. A general procedure for their synthesis was developed. *N*-Alkyl benzene and ethyl butyrylacetate were used as starting materials. The purification of reaction intermediates was not necessary if preparative hplc was used to purify the final products. Very pure materials were obtained with good yield. Their structure was confirmed by carbon 13 nmr.

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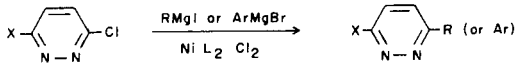
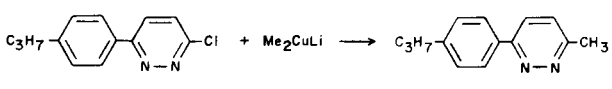
In 1938, Wongard and Lanzendorf [1] first described the preparation of 3,6-bis-(4-*n*-alkylphenyl)pyridazines and the fact that they exhibited a liquid crystal phase. Later, Schubert and Koch [2] reported the synthesis of 3,6-bis-(4-*n*-alkoxyphenyl)pyridazines. Then, Zachke *et al.* [3] reported the synthesis of 3-alkoxy-6-phenylpyridazines. It seemed of interest to extend these studies to synthesize 3-aryl-6-(substituted-phenyl)pyridazines and examine their properties, since such compounds could have interesting liquid crystal phases and dielectric properties.

Compared to other heterocylic liquid crystals, the literature on pyridazines is rather sparse (the report of Schadt *et al.* [4] on 3-pentylcyclohexanyl-6-*n*-propylpyridazine first appeared after the completion of our synthetic work). The lack of attention to the pyridazines in the literature may be due to the fact that the general techniques used to introduce alkyl or aryl groups into other heterocyclic systems, are not very successful for pyridazines. Ohsawa *et al.* [5] reported that they have succeeded in the alkylation and arylation of pyridazines when a cross coupling reaction is conducted in the presence of nickel-phosphine complexes.

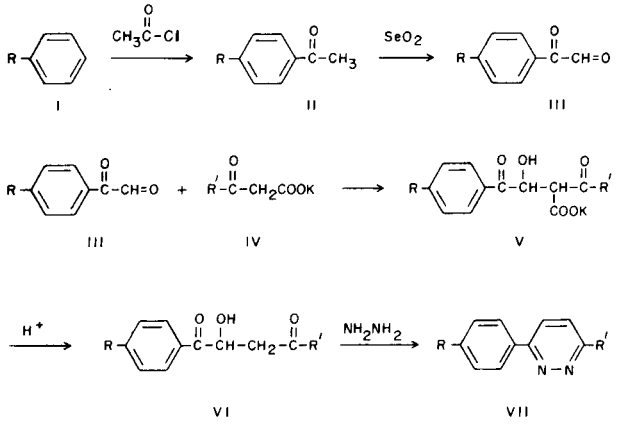


The yields for their examples were in the acceptable range of 71-74% when R is a methyl group. However, when R is an ethyl group, the yields dropped to only 20-38%.

We tried a similar cross coupling reaction using lithium dimethylcuprate to try to make 3-(4-*n*-propylphenyl)-6-methylpyridazine. However, the yield was poor and purification of the product was difficult.



Levisalles [6] reported a method for synthesizing 3-phenyl-6-methylpyridazine. We discovered that by a modification of this method, we could make 3-aryl-6-alkylpyridazines in good yield with an easy purification. We also found out that, when preparative hplc is used to purify the final product, it is not necessary to purify most of the intermediates. This makes this synthetic route as described below, even more attractive.



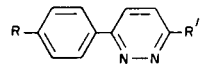
The selenium dioxide oxidation reaction (II → III) is easily conducted, but purification of the ketoaldehyde III is difficult. Vacuum distillation is effective for purification when R = H [7], but becomes increasingly difficult with larger R groups. When R = hexyl or heptyl, distillation leads to decomposition.

The ^{13}C nmr spectrum of the crude product (III, R = butyl) shows three signals in the carbonyl region. Also, the ^{1}H nmr spectrum shows a split of the aldehyde proton signal. This could be the result of a partial polymerization of the aldehyde. If this is the case it might be possible to use the crude product in the condensation step (III → V), assuming the polymer will regenerate the monomer when the monomer becomes depleted. This type of condensation is well known [8], but with long R and R′ groups we cannot expect a good yield without a suitable solvent. Dioxane is very appropriate in this case since it can dissolve the organic compounds as well as being able to mix with the water solution of the keto acid salt.

After acidification and further processing as described in the experimental paragraph the crude product VI was

Table I

Physical and Analytical Data on the Compounds Prepared



Tek No.	R	R'	Mp °C	Yield % [a]	Formula	MW	Calcd. % C	H	N	Found % C	H	N
2056	*n*-propyl	methyl	84.5-88	15 [b]	$C_{14}H_{16}N_2$	212.3	79.21	7.60	13.19	79.38	7.60	13.16
2057	*n*-butyl	*n*-propyl	87-88	28	$C_{17}H_{22}N_2$	254.4	80.27	8.72	11.01	80.42	8.84	11.01
2058	*n*-propyl	*n*-propyl	86-88	31.5	$C_{16}H_{20}N_2$	240.35	79.96	8.39	11.65	80.20	8.50	11.55
2059	*n*-pentyl	*n*-propyl	79-81.5	40	$C_{18}H_{24}N_2$	268.4	80.55	9.01	10.44	80.78	9.00	10.29
2060	*n*-hexyl	*n*-propyl	72-73	42	$C_{19}H_{26}N_2$	282.4	80.80	9.28	9.92	80.95	9.38	9.89
2061	*n*-heptyl	*n*-propyl	66-68	39	$C_{20}H_{28}N_2$	296.5	81.03	9.52	9.45	81.33	9.66	9.48
2062	*n*-octyl	*n*-propyl	73-75.5	46.5	$C_{21}H_{30}N_2$	310.5	81.24	9.74	9.02	81.08	9.82	8.95
2063	*n*-nonyl	*n*-propyl	69-71.5	46	$C_{22}H_{32}N_2$	324.5	81.43	9.94	8.63	81.56	10.09	8.63
2066	*n*-decyl	*n*-propyl	71-73	48	$C_{23}H_{34}N_2$	338.5	81.60	10.12	8.28	81.53	10.26	8.15

[a] Based on substituted acetophenone. [b] Based on propylbenzene and different route.

obtained and its ^{13}C nmr spectrum was taken (IV, R = butyl; 208.14, 200.06, 149.8, 131.3, 128.9, 128.6, 70.1, 47.6, 45.9, 35.8, 33.1, 22.3, 17, 13.9, 13.6). The two carbonyl carbons at 208 and 200, and the hydroxy carbon at 70, provide evidence that the assignment of structure VI is correct. Since the crude product IV is reasonably pure, we were able to use it for the cyclization step (VI → VII) without further purification. Purification of VII by preparative hplc (using normal phase silica gel column and 30% ethyl acetate in hexane for the mobile phase) gave a product which could be further purified by recrystallization from hexane. Nine variously-substituted pyridazines were synthesized in this manner. The melting points, yields, and elemental analysis for these nine compounds are presented in Table I and their ^1H and ^{13}C nmr data are presented in Tables II and III.

Table II

NMR Data (Deuteriochloroform) on the Compounds Prepared

Tek No.	Chemical shift ppm
2056	7.9 (d, 2H, Ar), 7.68 (3, 1H, Ar), 7.25 (d, 2H, Ar), 7.2 (d, 1H, Ar), 2.7 (s, 3H), 2.6 (t, 2H), 1.6 (sextet, 2H), 0.9 (t, 3H)
2057	8.0 (d, 2H, Ar), 7.71 (d, 1H, Ar), 7.3 (d, 3H, Ar), 3.0 (t, 2H), 2.68 (t, 2H), 0.9-3.0 (m, 12H)
2058	8.0 (d, 2H, Ar), 7.71 (d, 1H, Ar), 7.3 (d, 3H, Ar), 2.98 (t, 2H), 2.65 (t, 2H), 1.75 (octet, 4H), 0.8-1.1 (m, 6H)
2059	8.0 (d, 2H, Ar), 7.73 (d, 1H, Ar), 7.3 (d, 3H, Ar), 2.97 (t, 2H), 2.65 (t, 2H), 0.8-2.1 (m, 14H)
2060	8.0 (d, 2H, Ar), 7.72 (d, 3H, Ar), 2.95 (t, 2H), 2.65 (t, 2H), 0.8-2.0 (m, 16H)
2061	7.95 (d, 2H, Ar), 7.71 (d, 1H, Ar), 7.28 (d, 3H, Ar), 2.95 (t, 2H), 2.65 (t, 2H), 0.8-2.0 (m, 18H)
2062	7.95 (d, 2H, Ar), 7.7 (d, 1H, Ar), 7.28 (d, 3H, Ar), 2.92 (t, 2H), 2.65 (t, 2H), 0.8-2.0 (m, 20H)
2063	7.95 (d, 2H, Ar), 7.72 (d, 1H, Ar), 7.28 (d, 3H, Ar), 2.95 (t, 2H), 2.65 (t, 2H), 0.8-2.0 (m, 22H)
2066	8.0 (d, 2H, Ar), 7.72 (d, 1H, Ar), 7.3 (d, 3H, Ar), 2.97 (t, 2H), 2.68 (t, 2H), 0.8-2.1 (m, 24H)

Table III

^{13}C NMR Data (Deuteriochloroform) on the Compounds Prepared

Tek No.	Chemical Shift [a]
2056	158.2, 156.8, 144.6, 134, 2 × 129.2, 2 × 127, 126.7, 123.6, 37.8, 24.3, 21.9, 13.7
2057	161.8, 157.3, 144.8, 133.9, 2 × 129, 2 × 126.8, 126.6, 123.6, 37.9, 35.4, 33.4, 22.7, 22.3, 13.9, 13.7
2058	161.8, 157.3, 144.6, 134, 2 × 129, 2 × 126.7, 126.5, 123.6, 37.9, 37.8, 24.3, 22.7, 2 × 13.7
2059	161.7, 157.3, 144.8, 134, 2 × 129, 2 × 126.8, 126.5, 123.5, 37.9, 35.7, 31.5, 30.9, 22.5, 13.9, 13.7
2060	161.7, 157.2, 144.8, 133.9, 2 × 129, 2 × 126.8, 126.5, 123.5, 37.9, 35.8, 31.7, 31.2, 29, 22.7, 22.6, 14, 13.7
2061	161.8, 157.3, 144.9, 133.9, 2 × 129, 2 × 126.8, 126.5, 123.6, 37.9, 35.8, 31.8, 31.3, 29.3, 2 × 29.1, 22.7, 14, 13.7
2062	161.8, 157.3, 144.9, 133.9, 2 × 129, 2 × 126.8, 126.5, 123.5, 37.9, 35.8, 31.8, 31.3, 2 × 29.5, 29.3, 22.8, 22.7, 14, 13.7
2063	161.7, 157.2, 144.8, 133.9, 2 × 129, 2 × 126.7, 126.5, 123.5, 37.9, 35.8, 31.8, 31.3, 2 × 29.5, 2 × 29.3, 2 × 22.6, 14, 13.7
2066	161.8, 157.3, 144.9, 133.9, 2 × 129, 2 × 126.7, 126.5, 123.5, 37.9, 35.8, 31.9, 31.3, 2 × 29.6, 3 × 29.3, 22.7, 22.6, 14, 1
2015	162, 157.2, 144.9, 134, 2 × 129, 2 × 126.8, 126.5, 123.6, 35.9, 35.7, 2 × 31.4, 30.9, 2 × 29.2, 2 × 13.99

[a] If there are two or three carbons with the same chemical shift it is expressed as 2 ×, or 3 ×.

EXPERIMENTAL

The final compounds were purified on a water 500A preparative hplc

instrument. The structure of the products were established by their ^{13}C and ^{1}H nmr spectra taken on a Jeol FT 90 Q Fourier Transform nmr spectrometer and by ir spectroscopy. The purity of the final products was checked on a Perkin-Elmer series 10 analytical hplc instrument.

Using 3-(4-*n*-nonylphenyl)-6-*n*-propylpyridazine as an example, the general experimental procedure used is as follows.

4-*n*-Nonylacetophenone (II, R = *n*-nonyl).

Anhydrous aluminum trichloride (6.5 g) was mixed with 200 ml of methylene chloride by stirring at room temperature. A solution of 8 g of *n*-nonylbenzene, 4 ml of acetyl chloride, and 10 ml of methylene chloride was added dropwise with stirring to this mixture. After the resulting mixture had been stirred for two hours, the slightly yellow solution was poured into about 500 ml of ice and acidified with 15 ml of aqueous hydrochloric acid. The organic layer was separated, washed twice with water, dried over magnesium sulfate and concentrated to give 8.86 g (91%) of an oily product. Its ^{13}C nmr spectrum is in accord with its assigned structure (δ 197.5, 148.5, 135, 129.2, 128.9 and 9 carbons between 14-36). For the preparation of an aqueous solution of the potassium salt of 3-oxohexanoic acid (IV, R' = **n**-propyl), the same method as described by Schechter *et al.* [19] was used.

3-(4-*n*-Nonylphenyl)-6-*n*-propylpyridazine (VII, R = *n*-nonyl, R' = *n*-propyl).

Selenium dioxide (3.6 g), water (3 ml), and dioxane (30 ml) were mixed, stirred and heated until the white crystals dissolved. About 8 g of 4-*n*-nonylacetophenone was added to the mixture which was boiled under reflux for three hours. After the mixture had been cooled, the black precipitate was removed by filtration and the yellow filtrate was diluted with 100 ml of dioxane and mixed with the aqueous solution of the potassium 3-oxohexanoate (made from 5 ml of ethyl butyroacetate and 2.4 g of potassium hydroxide in 20 ml of water, hydrolysis for 3 days at 0-5° and then saturated by carbon dioxide). The reaction mixture was kept at 0-5° for four days. Then 20% hydrochloric acid (10 ml) was added and it was concentrated to remove the dioxane. The residue was dissolved in 100 ml of toluene and washed twice with water, dried over magnesium sulfate and filtered. Hydrazine monohydrate (3 ml) was added to the toluene filtrate and the mixture was boiled under reflux for 3 hours. The toluene solution was washed twice with water, dried over magnesium sulfate and concentrated. The residue was dissolved in a 1:3 mixture of ethyl acetate and hexane, injected in a preparative hplc column using the same solvent for the mobile phase. The compound corresponding to the main hplc peak was separated out and recrystallized from hexane. About 4.8 g (46%, based on *n*-nonylacetophenone) was obtained (the mother liquor was not treated). Its ^{1}H and ^{13}C nmr spectra are summarized in Tables II and III. With a Perkin-Elmer C18 5 micro reverse phase column, 90% methanol-water for the mobile phase, only one peak was observed.

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