Pyridazines. LXVIII [1]. Convenient Synthesis of Phenyl (6-Substituted 3-Pyridazinyl) Ketones *via* the Oxidative Decyanation Route

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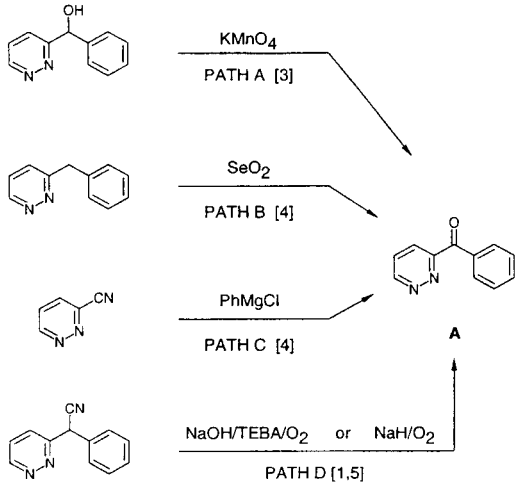
Received August 17, 1993

A convenient approach to aryl 3-pyridazinyl ketones **4**, **7-10** bearing various O-, N-, or C-substituents at C-6 of the diazine nucleus *via* oxidative decyanation of appropriate aryl-heteroaryl-acetonitriles is proposed.

J. Heterocyclic Chem., **30**, 1685 (1993).

So far, several synthetic routes to phenyl 3-pyridazinyl ketone (**A**), which represents a valuable synthetic building block, have been described in the literature (see Scheme 1) [1,3-5]. Whereas pathways A-C may be considered as appropriate routes also for the preparation of aryl 3-pyridazinyl ketones bearing additional substituents in the carbocyclic moiety, they appear to be less suitable for the synthesis of congeners of **A** being substituted at C-6 of the pyridazine nucleus. The latter compounds now were required for our ongoing studies directed towards the preparation of pyridazine congeners of bio-active molecules.

Scheme 1



Based on recent findings that the ketone **A** can be conveniently prepared also from phenyl 3-pyridazinyl acetonitrile by oxidative decyanation (Scheme 1, Path D) [1,5], we now considered the corresponding 6-chloro derivative **2** as a potentially useful starting material for the synthesis of the title compounds.

Treatment of the chloronitrile **2** (conveniently available from 3,6-dichloropyridazine **1** [1,6]) in dimethyl sulfoxide solution with 50% aqueous sodium hydroxide in the presence of the phase transfer catalyst triethylbenzylammonium chloride (TEBA), passing oxygen gas through the solution, was found to afford the chloro ketone **3** in satisfactory yield [7]. Compound **3**, which has been obtained recently also by an alternative route [9], could be transformed into the dimethylaminoethoxy derivative **7** upon action of the appropriate sodium alcoholate. An even more convenient access to phenyl 6-alkoxy-3-pyridazinyl ketones (which was developed in view of the smooth replacement of chlorine in halopyridazines by *O*-nucleophiles [10]) consists in treatment of **2** with sodium hydroxide/oxygen/TEBA using the appropriate alcohol as the solvent. As shown in the high-yield one-pot transformation of **2** into the methoxy ketone **4**, under these conditions, oxidative decyanation and substitution of the chloro function occur simultaneously. The corresponding alcohol **5** is obtained quantitatively upon sodium borohydride reduction of **4**.

Similarly, we prepared 6-(α-hydroxybenzyl)-3(2*H*)-pyridazinone (**6**) by reacting **2** under analogous conditions in aqueous medium and subsequent reduction of the ketone thus formed.

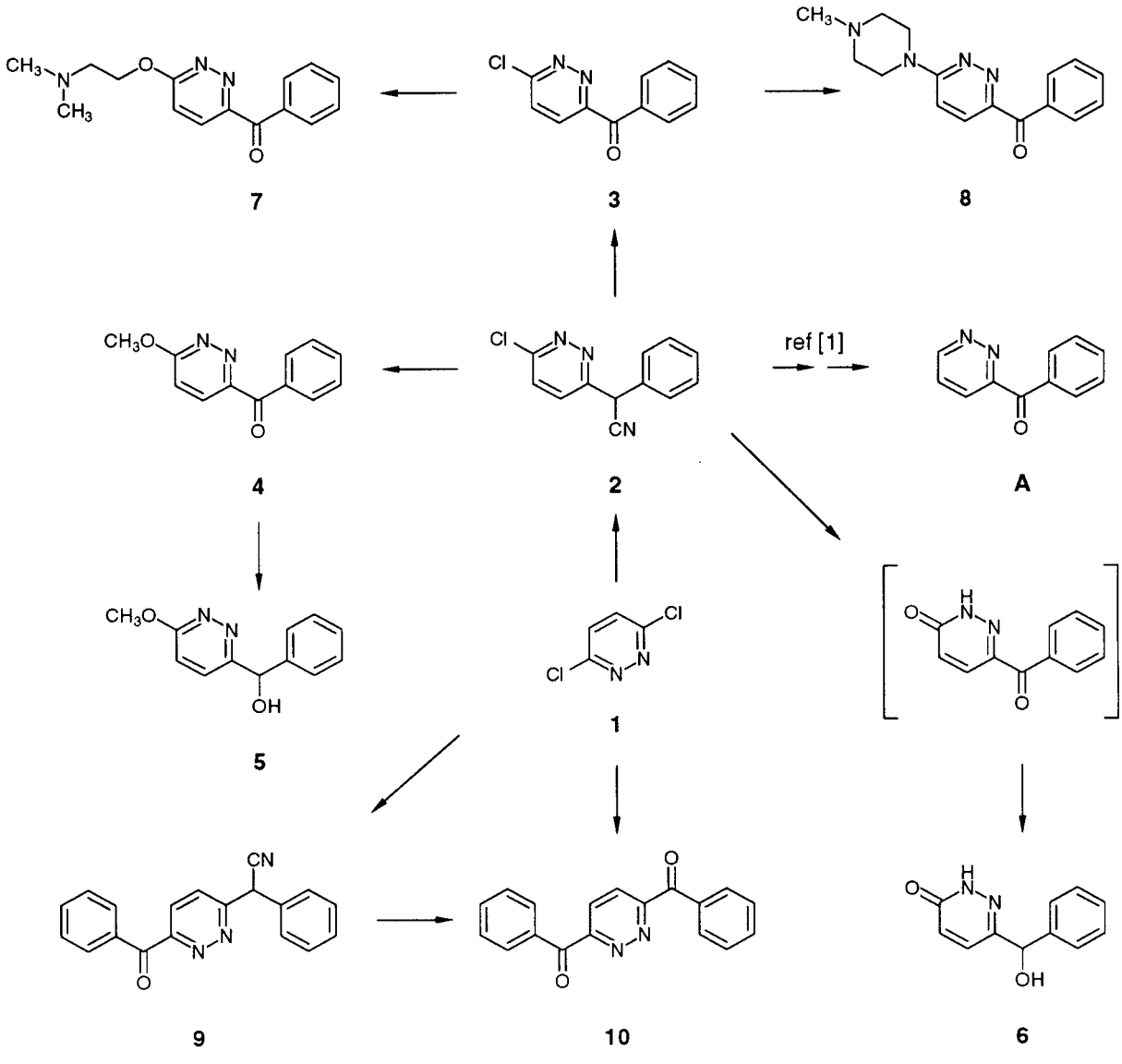
Starting from the chloro ketone **3**, also phenyl 3-pyridazinyl ketones bearing a substituted amino function at pyridazine C-6 are conveniently accessible as exemplified in the synthesis of compound **8**. Reductive dehalogenation of **3** (ammonium formate/Pd/C) led to phenyl 3-pyridazinyl ketone **A**, albeit in only 40% yield [11].

In a patent [3], it has been claimed that reaction of 3,6-dichloropyridazine (**1**) [13] with phenylacetonitrile (or 2-phenylpropionitrile)/50% aqueous sodium hydroxide in the presence of TEBA affords the nitrile **2** or the corresponding homologous compound, respectively [14]. We now found that in the case of the reaction of **1** with phenylacetonitrile, under these conditions, expectedly again oxidative decyanation occurs to give 3,6-dibenzoylpyridazine (**10**) but not the nitrile **2**. Under slightly modified conditions, also the intermediate (6-benzoyl-3-pyridazinyl)phenylacetonitrile (**9**) could be isolated from the reaction mixture, along with the nitrile **2** and the ketone **3**.

Spectral and analytical data of all new compounds are summarized in Table 1.

The results obtained clearly demonstrate the utility of oxidative decyanation of diarylacetonitriles [5,8,15] also for the synthesis of aryl 3-pyridazinyl ketones bearing *O*-, *N*-, or *C*-substituents at C-6 of the 1,2-diazine nucleus.

Scheme 2



EXPERIMENTAL

Melting points were determined on a Kofler hot-stage microscope and are uncorrected. The ir spectra (potassium bromide) were recorded on a Jasco IRA-1 spectrometer. The glc/ms analyses were carried out on a Hewlett-Packard 5890A/5970B-GC/MSD instrument. The ^{1}H-nmr spectra were obtained on a Varian EM 390 (90 MHz) or on a Bruker AC 80 (80.13 MHz). Chemical shifts are reported in ppm downfield from TMS as an internal standard and are given in δ units. Column chromatography was performed on Kieselgel 60 (70-230 mesh; Merck). Elemental analyses were carried out by Mikroanalytisches Laboratorium, Institute of Physical Chemistry, University of Vienna. For yields, melting points, elemental analyses and spectral data of compounds **4-10** see Table 1.

3-(6-Chloropyridazinyl) Phenyl Ketone (**3**).

A solution of **2** (2.30 g, 10 mmoles) [1,6], triethylbenzylammonium chloride (0.23 g, 1 mmole), and 50% aqueous sodium hydroxide (1.63 g) in dimethyl sulfoxide (100 ml) was stirred at room temperature for 3 hours, passing a strong stream of oxygen through it. Then water was added (60 ml) and the mixture was brought to *p*H 7 with 2*N* sulphuric acid and extracted exhaustively with dichloromethane. The combined organic layers were dried over anhydrous sodium sulphate and evaporated *in vacuo*.

Table 1

Yields and Analytical Characterization of Compounds **4-10**

No.	Yield (%) [a]	Mp (°C) (recryst-alization solvent)	Molecular Formula (M/W)	Elemental Analyses Calcd.%/Found% C	H	N	^{1}H NMR (deuteriochloroform) δ (ppm) Pyridazine H-4 (d, 1H)	H-5 (d, 1H)	$^3J_{4,5}$ (Hz)	Other	IR (cm^{-1})	MS (EI 70 eV) m/z (%)
4	58	115-118 (ethanol)	$C_{12}H_{10}N_2O_2$ (214.23)	67.28 67.07	4.71 4.46	13.08 13.04	8.14	7.43	9	4.15 (s, OCH_3, 3H), 7.96-8.08 (m, Ph-2,6, 2H), 7.54-7.71 (m, Ph-3,4,5, 3H)	1645 s, 1580 s, 1460 m, 1350s, 1310 s, 1270 s	77 (100), 105 (74), 171 (87) 186 (62), 213 (38), 214 (53)
5	96	64-66 (cyclohexane)	$C_{12}H_{12}N_2O_2$ (216.24)	65.29 65.18	5.71 5.52	12.69 [c] 12.83	7.29	6.91	9	7.25-7.51 (m, Ph, 5H), 4.11 (s, OCH_3, 3H) 5.93 (s, OH, 1H)	3400 m, 3000 m, 1720 m, 1460 s, 1390 s, 1300 s	77 (51), 79 (28), 105 (22), 139 (24), 199 (41), 216 (100)
6	52	175-177 (ethanol)	$C_{11}H_{10}N_2O_2$ (202.21)	65.34 65.47	4.98 4.68	13.85 13.90	7.41	6.83	10	7.28-7.40 (m, Ph, 5H), 5.54 (d, J = 4 Hz, C*H*OH, 1H), 6.22 (d, J = 4Hz, OH, 1H), 12.81 (s, NH, 1H) [e]	3190 s, 2820 m, 1650 s, 1590 s, 1420 m, 1040 s	51 (52), 77 (86), 79 (64), 97 (94), 105 (100), 124 (35), 202 (75)
7	61	[b]	$C_{15}H_{17}N_3O_2$ (271.32)	65.53 65.28	6.38 6.23	15.28 [d] 15.55	8.13	7.18	9	8.09-8.30 (m, Ph-2,6, 2H), 4.75 (t, J = 5Hz), CH_2O, 2H), 7.27-7.65 (m, Ph-3,4,5,3H), 2.81 (t, J = 5 Hz, CH_2N, 2H), 2.35 (s, CH_3, 6H)	2970 w, 1590 m, 1410 m, 1060 m	54 (89), 71 (100), 105 (9) 227 (2), 271 (1)
8	77	99-102 (cyclohexane)	$C_{16}H_{18}N_4O$ (282.35)	68.06 68.18	6.43 6.67	19.84 19.86	8.05	7.00	9	8.15-8.30 (m, Ph-2,6, 2H), 2.38 (s, NCH_3, 3H), 7.41-7.63 (m, Ph-3,4,5, 3H), 2.45-2.65, 3.89-3.99 (m, piperazine, 8H)	2800 m, 2790 m, 1650 s, 1565 s, 1370 m, 1220 s	70 (100), 77 (24), 83 (73) 105 (26), 212 (39), 282 (10)
9	26	186-188 (ethanol)	$C_{19}H_{13}N_3O$ (299.33)	76.24 76.00	4.38 4.18	14.04 14.05	7.56	8.29	8	7.25-8.18 (m, Ph, 10H), 6.39 (s, PhCH, 1H) [e]	3200 s, 2190 m, 1640 m, 1605 s, 1390 m, 1250 s	77 (89), 105 (71), 155 (71), 244 (61), 298 (55), 299 (100)
10	48 [f] 89 [g]	127-129 (ethanol)	$C_{18}H_{12}N_2O_2$ (288.31)	74.41 74.25	4.25 4.06	9.64 [h] 9.67	8.38	8.38	--	8.20-8.32 (m, Ph- 2,2',6,6', 4H) 7.41-7.66 (m, Ph-3,3',4,4',5,5',6H)	3050 w, 1650 s, 1580 m, 1560 m, 1280 s, 1150 m	77 (87), 105 (100), 155 (64), 260 (17), 288 (32)

[a] Yields not optimized. [b] Oil. [c] Calculated for $C_{12}H_{12}N_2O_2 \cdot 1/4H_2O$. [d] Calculated for $C_{15}H_{17}N_3O_2 \cdot 1/5H_2O$. [e] Recorded from a hexadeuteriodimethyl sulfoxide solution. [f] Method A, see Experimental. [g] Method B, see Experimental. [h] Calculated for $C_{18}H_{12}N_2O_2 \cdot 1/8H_2O$.

The residue was subjected to column chromatography using dichloromethane as the eluent and was then recrystallized from ethanol to yield 1.18 g (54%) of analytically pure **3** [9].

3-(6-Methoxypyridazinyl) Phenyl Ketone (**4**).

A solution of **2** (2.30 g, 10 mmoles) [1,6], triethylbenzylammonium chloride (0.23 g, 1 mmole), and 50% aqueous sodium hydroxide (1.63 g) in methanol (100 ml) was stirred at room temperature for 3 hours, passing a strong stream of oxygen through it. Then water was added (60 ml) and methanol was evaporated *in vacuo*. The mixture was adjusted to *p*H 7 with 2*N* sulphuric acid and extracted exhaustively with dichloromethane. The combined organic layers were dried over anhydrous sodium sulphate and evaporated *in vacuo*. The residue was recrystallized from ethanol/charcoal to yield 1.24 g of **4**.

3-(6-Methoxypyridazinyl)phenylmethanol (**5**).

To a solution of **4** (2.14 g, 10 mmoles) in methanol (120 ml), sodium borohydride (0.10 g, 2.5 mmoles) was added within 15 minutes and the mixture was stirred at room temperature for 1 hour. Then it was acidified with 2*N* sulphuric acid and methanol was removed *in vacuo*. The ice-cooled solution was made alkaline by addition of 50% aqueous sodium hydroxide and was then extracted exhaustively with dichloromethane. The organic layers were dried over anhydrous sodium sulphate and were then evaporated *in vacuo*. The residue was subjected to column chromatography using ethyl acetate as the eluent to yield 2.08 g of **5**.

6-(α-Hydroxybenzyl)-3(2*H*)-pyridazinone (**6**).

A mixture of **2** (0.23 g, 1 mmole), triethylbenzylammonium chloride (0.02 g, 0.1 mmole), and 50% aqueous sodium hydroxide (1.63 g) was stirred at room temperature for 3 hours passing a strong stream of oxygen through it. Then water was added (60 ml), the mixture was adjusted to *p*H 7 with 2*N* sulphuric acid and was extracted exhaustively with dichloromethane. The combined organic layers were dried over anhydrous sodium sulphate and were then evaporated *in vacuo*. The residue was taken up in methanol (30 ml) and sodium borohydride (0.05 g, 1.25 mmoles) was added within 15 minutes. After 1 hour of stirring at room temperature, the mixture was acidified with 2*N* sulphuric acid and methanol was removed *in vacuo*. The ice-cooled solution was made alkaline by addition of 50% aqueous sodium hydroxide and was then extracted exhaustively with dichloromethane. The organic layers were dried over anhydrous sodium sulphate and were then evaporated *in vacuo*. The residue was subjected to column chromatography using ethyl acetate as the eluent to yield 105 mg of **6** (52% yield related to **2**).

3-[6-(2-Dimethylamino)ethoxypyridazinyl] Phenyl Ketone (**7**).

To a solution of **3** (0.44 g, 2 mmoles) in 2-dimethylaminoethanol (10 ml), sodium hydride (80% in paraffin, 0.06 g, 2 mmoles) was added under an argon atmosphere. The mixture was stirred for 30 minutes at room temperature, then excess 2-dimethylaminoethanol was removed *in vacuo*. The residue was suspended in a minimum of water and the mixture was exhaustively extracted with dichloromethane. The combined organic layers were dried over anhydrous sodium sulphate and were then evaporated *in vacuo*. The residue was subjected to column chromatography using dichloromethane/methanol (9 + 1) as the eluent to yield 331 mg of **7**.

3-[6-(4-Methylpiperazinyl)pyridazinyl] Phenyl Ketone (**8**).

A solution of **3** (2.19 g, 10 mmoles) in 4-methylpiperazine (20 ml) was refluxed for 6 hours. The residue obtained after evaporation *in vacuo* was suspended in a minimum of water. After exhaustive extraction with dichloromethane, the combined organic layers were dried over anhydrous sodium sulphate and evaporated *in vacuo*. Recrystallization from cyclohexane afforded 2.17 g of **8**.

(6-Benzoyl-3-pyridazinyl)phenylacetonitrile (**9**).

A mixture of **1** (1.00 g, 6.71 mmoles), phenylacetonitrile (1.00 g, 8.55 mmoles), triethylbenzylammonium chloride (0.01 g, 0.04 mmole), and 50% aqueous sodium hydroxide (2 ml) was stirred for 30 minutes at room temperature. Then additional triethylbenzylammonium chloride (0.01 g, 0.04 mmole) was added and stirring was continued for 14 hours. The mixture was then poured into dichloromethane (40 ml). The organic layer was separated, washed with water, dried over anhydrous sodium sulphate and evaporated *in vacuo*. The residue was subjected to column chromatography using ethyl acetate as the eluent, yielding 0.99 g (26%) of **9** as fraction II. From fraction I, 0.32 g (21%) of **2**, from fraction III, 0.35 g (24%) of **3** were isolated.

3,6-Dibenzoylpyridazine (**10**).

Method A.

A mixture of **1** (7.20 g, 58.67 mmoles), phenylacetonitrile (7.20 g, 61.56 mmoles), triethylbenzylammonium chloride (0.25 g, 1.09 mmoles), and 50% aqueous sodium hydroxide (7.5 ml) was stirred for 30 minutes at room temperature. Then additional triethylbenzylammonium chloride (0.25 g, 1.09 mmoles) was added and stirring was continued for 48 hours. The mixture was then poured into dichloromethane (150 ml). The organic layer was washed with water, dried over anhydrous sodium sulphate and evaporated *in vacuo*. The residue was recrystallized from ethanol to yield 8.11 g of **10**.

Method B.

A mixture of **9** (0.30 g, 1 mmole), triethylbenzylammonium chloride (0.01 g, 0.04 mmole), and 50% aqueous sodium hydroxide (2 ml) was stirred for 24 hours at room temperature. Then the mixture was poured into dichloromethane (20 ml). The organic layer was washed with water, dried over anhydrous sodium sulphate and evaporated *in vacuo*. The residue was recrystallized from ethanol to yield 0.26 g of **10**.

REFERENCES AND NOTES

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[2] Taken in part from the Ph.D. Thesis of T. Langer, University of Vienna, 1991.

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[6] T. Yamada, Y. Nobuhara, H. Shimamura, K. Yoshihara, A. Yamaguchi and M. Ohki, *Chem. Pharm. Bull.*, **29**, 3433 (1981).

[7] Initial attempts to convert **2** into **3** under the conditions given in ref [8] (toluene solution, 50% aqueous sodium hydroxide, TEBA, air) resulted in the formation of polymeric products only.

[8] C. K. F. Hermann, Y. P. Sachdeva and J. F. Wolfe, *J. Heterocyclic Chem.*, **24**, 1061 (1987).

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[11] As a side reaction, reduction of the oxo function is observed. Moreover, thermally induced dismutation [12] of the thus resulting alcohol occurs owing to the elevated temperature required for reductive dehalogenation. Similarly, we did not succeed in enhancing the yield of **A** by using H_2/Pd/C.

[12] G. Heinisch and T. Huber, *Liebigs Ann. Chem.*, 19 (1992).

[13] R. H. Mizzoni and P. E. Spoerri, *J. Am. Chem. Soc.*, **73**, 1873 (1951).

[14] Only for the synthesis of the latter compound, experimental details are provided in this patent.

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