Phase-Transfer Catalyzed *N*-Alkylation of 3(2*H*)-Pyridazinones (3-Oxo-2,3-dihydropyridazines)

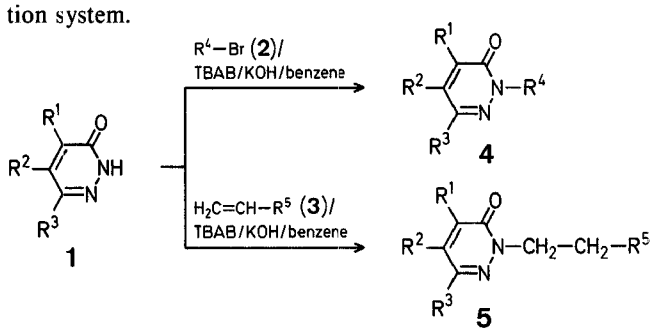
Toshihiro YAMADA*, Masahiko OHKI

Research Laboratories, Morishita Pharmaceutical Co., Ltd., 1658, Oh-shinohara, Yasu-cho, Yasu-gun, Shiga, 520-23, Japan

During the past decade, phase-transfer catalysis has been found to be a useful technique in heterogeneous reactions[1]. Application of this technique to the *N*-alkylation of amides such as acylanilines[2], lactams[3,4], *N*-substituted formamides[5], *N*-substituted carboxamides[6], and naphthylcarbamates[7] has been reported. In the course of synthetic studies on 3-oxo-2,3-dihydropyridazine [3(2*H*)-pyridazinone] derivatives we have also applied this method to the *N*-alkylation of 3(2*H*)-pyridazinones and have found that the reaction proceeds satisfactorily under mild condition in a heterogeneous reaction system under phase-transfer catalysis.

Alkylations of 3(2*H*)-pyridazinones with alkyl halides have hitherto been carried out in the presence of metallic sodium in absolute ethanol[8,9,10] or sodium hydride in aprotic polar solvents such as dimethylformamide[11]. However, these classical alkylating reactions require strong basic conditions, high temperature, and rather long reaction times and are therefore not appropriate for the alkylation of compounds which contain sensitive groups.

In the present study, 3(2*H*)-pyridazinones **(1)** were alkylated by various types of alkyl bromides **(2)** and Michael acceptors **(3)** in the presence of tetrabutylammonium bromide (TBAB) as a phase-transfer catalyst in a two-phase solid/liquid reaction system.



With primary and secondary alkyl bromides **(2)**, good yields of alkylation products **(4)** are obtained in all cases whereas the method is not applicable to tertiary alkyl bromides. With 1,ω-dibromoalkanes, only monoalkylation products are obtained; this result is in contrast to the classical non-catalytic method (potassium hydroxide/dimethylformamide) which usually gives rise to contamination of the product with the bis-alkylation product. Further, the Michael reaction of substrates **1** with acrylonitrile (**3**, R^5 = —CN) or ethyl acrylate (**3**, R^5 = —$COOC_2H_5$) under catalytic phase-transfer conditions proceeds smoothly to afford the alkylation products **5** in high yield.

2-Alkyl-3-oxo-6-phenyl-2,3-dihydropyridazines; Typical Procedures:

Method A, using Alkyl Bromides:

3-Oxo-6-phenyl-2-(4-phthalimidobutyl)-2,3-dihydropyridazine: A mixture of 3-oxo-6-phenyl-2,3-dihydropyridazine (**1**, $R^1 = R^2 = R^3 = H$; 1.722 g, 0.01 mol), *N*-(4-bromobutyl)-phthalimide (**2**, R^4 = 4-phthalimidobutyl; 3.224 g, 0.01 mol), potassium hydroxide (0.562 g, 0.01 mol), and tetrabutylammonium bromide (0.565 g, 0.002 mol) in benzene (200 ml) is stirred at room temperature for 10 h. The organic layer is separated, washed with aqueous 5% sodium hydroxide (200 ml), 10% hydrochloric acid (180 ml), and water (200 ml), and is dried with sodium

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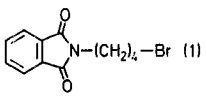
Table. Phase-Transfer Catalyzed *N*-Alkylation of 3-Oxo-6-phenyl-2,3-dihydropyridazines (**1**)

R^1	R^2	R^3	Alkylating agent (equiv.)	Method	Time [h]	Yield[a] [%]	m.p. [°C] or b.p. [°C]/torr[b]	Molecular[c] Formula or m.p. reported	^{1}H-N.M.R. (DMSO-d_6/TMS)[d] δ [ppm] (N—CH)
H	H	H	*n*-C_4H_9—Br (2)	A	5	73	89–90°/3	$C_8H_{12}N_2O$ (144.2)	4.04 (t, 2H, J=7 Hz)
Cl	Cl	H	*n*-C_4H_9—Br (2)	A	5	70	125–128°/0.8	$C_8H_{10}Cl_2N_2O$ (221.1)	4.10 (t, 2H, J=7 Hz)
Cl	OCH_3	H	*n*-C_4H_9—Br (2)	A	5	85	162–165°/2	$C_9H_{13}ClN_2O_2$ (215.7)	4.06 (t, 2H, J=7 Hz)
Cl		H	*n*-C_4H_9—Br (2)	A	5	69	215–220°/2	$C_{12}H_{18}ClN_3O$ (255.7)	4.00 (t, 2H, J=7 Hz)
H	H	CH_3	*n*-C_4H_9—Br (2)	A	5	79	105–107°/1.5	$C_9H_{14}N_2O$ (166.2)	3.96 (t, 2H, J=7 Hz)
H	H	$-COOC_2H_5$	*n*-C_4H_9—Br (2)	A	6	81	138–139°/2	$C_{11}H_{16}N_2O_3$ (224.3)	4.10 (t, 2H, J=7 Hz)
H	H		*n*-C_4H_9—Br (2)	A	6	46	163–164°/2	$C_{12}H_{17}N_3O_2$ (235.3)	4.08 (t, 2H, J=7 Hz)
H	H		*n*-C_4H_9—Br (2)	A	6	88	137–138°/1.5	$C_{10}H_{17}N_3O$ (195.3)	3.88 (t, 2H, J=7 Hz)
H	H	C_6H_5	*n*-C_4H_9—Br (2)	A	6	88	166–168°/3	$C_{14}H_{16}N_2O$ (216.3)	4.20 (t, 2H, J=7 Hz)
H	H	C_6H_5	*i*-C_4H_9—Br (2)	A	6	65	166–169°/2.5	$C_{14}H_{16}N_2O$ (216.3)	4.01 (t, 2H, J=7 Hz)
H	H	C_6H_5	*sec*-C_4H_9—Br (2)	A	6	68	166–168°/2	$C_{14}H_{16}N_2O$ (216.3)	5.10 (sextet, 1H, J=7 Hz)
H	H	C_6H_5	$H_3C-(CH_2)_7-Br$ (1)	A	6	80	183–185°/0.7	$C_{18}H_{24}N_2O$ (284.4)	4.15 (t, 2H, J=7 Hz)
H	H	C_6H_5	$H_3C-(CH_2)_{15}-Br$ (1)	A	6	83	68–70°	$C_{24}H_{40}N_2O$ (372.6)	4.16 (t, 2H, J=7 Hz)
H	H	C_6H_5	$C_6H_5-CH_2-CH_2-Br$ (1)	A	8	92	214–215°/1	$C_{18}H_{16}N_2O$ (276.3)	4.42 (t, 2H, J=7 Hz)
H	H	C_6H_5	$NC-(CH_2)_3-Br$ (1)	A	6	88	185–190°/0.3	$C_{14}H_{13}N_3O$ (239.3)	4.38 (t, 2H, J=7 Hz)
H	H	C_6H_5	$NC-(CH_2)_4-Br$ (1)	A	6	80	196–203°/0.7	$C_{15}H_{15}N_3O$ (253.3)	4.28 (t, 2H, J=7 Hz)
H	H	C_6H_5	$NC-(CH_2)_5-Br$ (1)	A	6	86	200–210°/0.7	$C_{16}H_{17}N_3O$ (267.3)	4.24 (t, 2H, J=7 Hz)
H	H	C_6H_5	 (1)	A	10	87	118–120°	$C_{22}H_{19}N_3O_3$ (373.4)	4.24 (t, 2H, J=7 Hz)
H	H	C_6H_5	$H_2C=CH-CH_2-Br$ (2)	A	6	82	163–165°/1.5	$C_{13}H_{12}N_2O$ (212.2)	4.68 (d, 2H, J=6 Hz)
H	H	C_6H_5	$C_6H_5-CH_2-Br$ (1)	A	8	89	90–91°	$C_{17}H_{14}N_2O$ (262.3)	5.38 (s, 2H,)
H	H	C_6H_5	$C_2H_5OOC-CH_2-Br$ (1)	A	8	81	99–100°	m.p. 100–102°[9]	4.96 (s, 2H,)
H	H	C_6H_5	$Br-(CH_2)_2-Br$ (3)	A	6	85	188–189°/0.6	$C_{12}H_{11}BrN_2O$ (279.1)	4.58 (t, 2H, J=7 Hz)
H	H	C_6H_5	$Br-(CH_2)_3-Br$ (3)	A	6	78	210–213°/0.8	$C_{13}H_{13}BrN_2O$ (293.2)	4.28 (t, 2H, J=7 Hz)
H	H	C_6H_5	$Br-(CH_2)_4-Br$ (3)	A	6	72	210–225°/2	$C_{14}H_{15}BrN_2O$ (307.2)	4.20 (t, 2H, J=7 Hz)
H	H	C_6H_5	$Br-(CH_2)_5-Br$ (3)	A	6	69	191–195°/1.5	$C_{15}H_{17}BrN_2O$ (311.2)	4.18 (t, 2H, J=7 Hz)
H	H	H	$H_2C=CH-CN$ (2)	B	5	89	75–76°	$C_7H_7N_3O$ (148.1)	4.39 (t, 2H, J=7 Hz)
Cl	Cl	H	$H_2C=CH-CN$ (2)	B	5	90	100–101°	m.p. 100°[12]	4.42 (t, 2H, J=7 Hz)
Cl		H	$H_2C=CH-CN$ (2)	B	5	83	101–102°	$C_{11}H_{13}ClN_3O_2$ (254.7)	4.38 (t, 2H, J=7 Hz)
H	H	CH_3	$H_2C=CH-CN$ (2)	B	5	88	96–97°	$C_8H_9N_3O$ (163.2)	4.33 (t, 2H, J=7 Hz)
H	H	C_6H_5	$H_2C=CH-CN$ (2)	B	8	95	103–104°	$C_{13}H_{11}N_3O$ (225.2)	4.46 (t, 2H, J=7 Hz)
H	H	C_6H_5	$H_2C=CH-COOC_2H_5$ (2)	B	8	86	199–202°/0.9	$C_{15}H_{16}N_2O_3$ (286.3)	4.41 (t, 2H, J=7 Hz)

[a] Yield of pure isolated products based on **1**.

[b] Melting points and boiling points are uncorrected.

[c] The microanalyses were in satisfactory agreement with the calculated values: C, ±0.26; H, ±0.30; N, ±0.28.

[d] The ^{1}H-N.M.R. spectra were measured at 100 MHz with a JEOL JNM-PS-100 Spectrometer.

sulfate. The solvent is removed under reduced pressure and the residue recrystallized from ethanol/diisopropyl ether to give the pure product; yield: 3.2 g (87%); m.p. 118–120 °C.

Method B, using Activated Ethylenes:

2-(2-Cyanoethyl)-3-oxo-6-phenyl-2,3-dihydropyridazine (**5**, $R^1=R^2=R^3=H$, $R^5=$—CN): A mixture of 3-oxo-6-phenyl-2,3-dihydropyridazine (**1**, $R^1=R^2=R^3=H$; 2.583 g, 0.015 mol), acrylonitrile (**3**, $R^5=$—CN; 1.593 g, 0.03 mol), potassium hydroxide (0.842 g, 0.015 mol), and tetrabutylammonium bromide (0.967 g, 0.003 mol) in benzene (100 ml) is stirred at room temperature for 8 h. The organic layer is separated, washed with aqueous 5% sodium hydroxide (100 ml), 10% hydrochloric acid (80 ml), and water (200 ml), and is dried with sodium sulfate. The solvent is removed under reduced pressure and the residue recrystallized from ethanol/diisopropyl ether to give the pure product; yield: 3.2 g (95%); m.p. 103–104 °C.

Classical Method:

1,4-Bis[3-oxo-6-phenyl-2,3-dihydro-2-pyridazinyl]-butane and 2-(4-Bromobutyl)-3-oxo-6-phenyl-2,3-dihydropyridazine: A mixture of 3-oxo-6-phenyl-2,3-dihydropyridazine (**1**, $R^1=R^2=R^3=H$; 17.22 g, 0.1 mol), 1,4-dibromobutane (21.6 g, 0.1 mol), potassium hydroxide (5.62 g, 30.1 mol), and dimethylformamide (150 ml) is stirred at 120 °C for 6 h. The mixture is then concentrated in vacuo and the residue extracted with chloroform (150 ml). The extract is washed with aqueous 5% sodium hydroxide (100 ml), 10% hydrochloric acid (70 ml), and water (200 ml), and is dried with sodium sulfate. The solvent is removed and the residue stirred with cold ethanol (300 ml). The precipitated *1,4-bis[3-oxo-6-phenyl-2,3-dihydro-2-pyridazinyl]-butane* is isolated by suction, washed with ethanol, and recrystallized from ethanol; yield: 15 g (25%); m.p. 195–198 °C. The ethanolic solution is concentrated in vacuo and the residue recrystallized from ethanol/diisopropyl ether to give *2-(4-bromobutyl)-3-oxo-6-phenyl-2,3-dihydropyridazine* as colorless crystals; yield: 19 g (21%); m.p. 42–43 °C; b.p. 220–225 °C/4 torr.

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* Address for correspondence.

1 C. M. Starks, C. Liotta, *Phase-transfer Catalysis: Principles and Techniques*, Academic Press Inc., New York, 1978.

2 R. Brehme, *Synthesis* **1976**, 113.

3 J. Palecek, J. Kuthan, *Z. Chem.* **17**, 260 (1977).

4 H. Takahata, T. Hashizume, T. Yamazaki, *Heterocycles* **12**, 1449 (1979).

5 T. Gajda, A. Koziara, S. Sawadzki, A. Zwierzak, *Synthesis* **1979**, 549.

6 A. Koziara, S. Zawadzki, A. Zwierzak, *Synthesis* **1979**, 527.

7 S. Julia, A. Ginebreda, *An. Quim.* **75**, 346 (1979).

8 J. A. King, F. H. McMillan, *J. Am. Chem. Soc.* **74**, 3222 (1952).

9 F. H. McMillan et al., *J. Am. Chem. Soc.* **78**, 407 (1956).

10 Y. Nitta, F. Yoneda, T. Ohtaka, T. Kato, *Chem. Pharm. Bull.* **12**, 69 (1964).

11 H. M. Holava, R. A. Partyka, *J. Med. Chem.* **14**, 262 (1971).

12 H. R. Hensel, H. Baumann, *German Patent (DBP)* 1420969 (1971), BASF; *C. A.* **75**, 118333 (1971).

0039-7881/81/0832-0633 $ 03.00