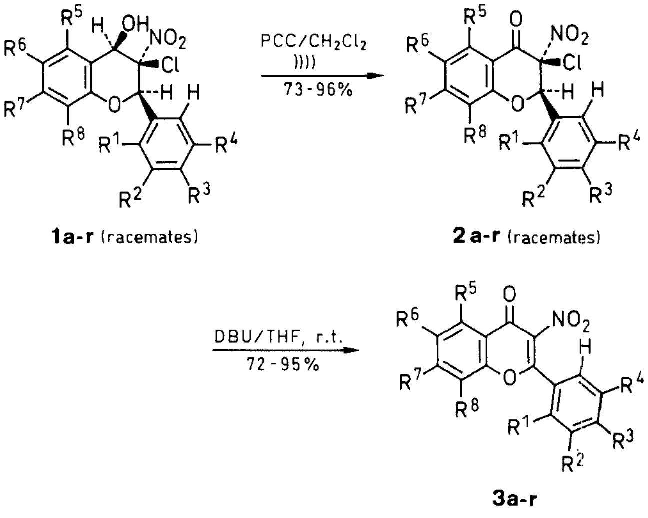
Synthesis of 2-Aryl-3-nitro-4*H*-1-benzopyran-4-ones

Daniel Dauzonne,* Cyrille Grandjean

Service de Chimie de l'Institut Curie, Section de Biologie, URA 1387 du CNRS, 26 rue d'Ulm, F-75231 Paris Cedex 05, France

Received 8 August 1991; revised 25 September 1991

2-Aryl-3-nitro-4*H*-1-benzopyran-4-ones (or 3-nitroflavones) **3** are conveniently prepared in good yields using a two-step approach starting from 2-aryl-3-chloro-3,4-dihydro-4-hydroxy-3-nitro-2*H*-1-benzopyrans **1**. A general synthesis of the novel 2-aryl-3-chloro-2,3-dihydro-3-nitro-4*H*-1-benzopyran-4-ones **2** employed as intermediates in the procedure is described.



1a-r (racemates)

2a-r (racemates)

3a-r

1-3	R^1	R^2	R^3	R^4	R^5	R^6	R^7	R^8
a	H	H	H	H	H	H	H	H
b	Cl	H	H	H	H	H	H	H
c	H	Cl	H	H	H	H	H	H
d	H	H	Cl	H	H	H	H	H
e	NO_2	H	H	H	H	H	H	H
f	H	NO_2	H	H	H	H	H	H
g	H	H	NO_2	H	H	H	H	H
h	OMe	H	H	H	H	H	H	H
i	H	OMe	H	H	H	H	H	H
j	H	H	OMe	H	H	H	H	H
k	H	OMe	OMe	OMe	H	H	H	H
l	H	H	Cl	H	OMe	H	H	H
m	H	H	Cl	H	H	OMe	H	H
n	H	H	Cl	H	H	H	OMe	H
o	H	H	Cl	H	H	H	H	OMe
p	H	H	Cl	H	H	Br	H	Br
q	H	H	Cl	H	H	Cl	H	H
r	H	H	Cl	H	H	NO_2	H	H

Flavonoids constitute an important class of compounds. Their chemistry, as well as their biological properties and pharmaceutical potencies have been widely investigated and extensively reviewed during the past thirty years.[1] However, little is known about flavones bearing a nitrogen atom in the 3-position. In this context, the development of a general approach to 3-nitroflavones appeared to be an attractive target.

In a recent paper, we have described a convenient method to prepare the 2-aryl-3-chloro-3,4-dihydro-4-hydroxy-3-nitro-2*H*-1-benzopyrans **1** as an enantiomeric mixture of the diastereoisomers having the relative configuration 2*R**, 3*R**, 4*R**.[2] We report herein that the compounds **1** are valuable starting materials to synthesize the title compounds **3** by a high-yield two-step process. The first stage involves a pyridinium chlorochromate (PCC) oxidation of **1** in dichloromethane, under sonochemical conditions, to lead to the hitherto unknown 2-aryl-3-chloro-2,3-dihydro-2-nitro-4*H*-1-benzopyran-4-ones **2** with the relative configuration 2*R**, 3*R**. These intermediates, on treatment with 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) in tetrahydrofuran at 20 °C, are then easily converted into the 3-nitroflavones **3** by elimination of a molecule of hydrochloric acid. It must be pointed out that the oxidation of **1** to **2** never goes to completion under mechanical stirring, even if a very large excess of PCC is used for a prolonged period of time.

Both steps of the synthetic pathway described in the present communication provide high yields. This route to 3-nitroflavones **3**, which has been performed with a wide

Table 1. 2-Aryl-3-chloro-2,3-dihydro-3-nitro-4*H*-1-benzopyran-4-ones **2** Prepared

Product	Reaction Time (h)	Yield[a] (%)	mp (°C)[b]	Molecular Formula[c]	IR ($CHCl_3$) $\nu_{C=O}$ (cm^{-1})	^1H NMR ($CDCl_3$/TMS) δ, J (Hz)
2a	8	85	107.5–108.5	$C_{15}H_{10}ClNO_4$ (303.7)	1714	6.26 (s, 1H, H-2), 7.07–7.81 (m, 8H_{arom}), 7.95–8.16 (m, 1H, H-5)
2b	8	89	139–140	$C_{15}H_9Cl_2NO_4$ (338.1)	1713	6.77 (s, 1H, H-2), 7.02–8.22 (m, 8H_{arom})
2c	8	82	106–107	$C_{15}H_9Cl_2NO_4$ (338.1)	1714	6.23 (s, 1H, H-2), 7.02–7.83 (m, 7H_{arom}), 7.95–8.15 (m, 1H, H-5)
2d	8	85	134–135	$C_{15}H_9Cl_2NO_4$ (338.1)	1713	6.23 (s, 1H, H-2), 7.05–7.35 (m, 2H_{arom}), 7.42 (br s, 4H_{arom}, C_6H_4Cl), 7.52–7.82 (m, 1H_{arom}), 7.95–8.15 (m, 1H, H-5)
2e	8	81	135–136	$C_{15}H_9ClN_2O_6$ (348.7)	1717	7.06–7.50 (m, 2H_{arom}), 7.23 (s, 1H, H-2), 7.50–8.20 (m, 6H_{arom})
2f	8	83	123–124	$C_{15}H_9ClN_2O_6$ (348.7)	1714	6.38 (s, 1H, H-2), 7.08–7.40 (m, 2H_{arom}), 7.45–7.87 (m, 3H_{arom}), 7.95–8.17 (m, 1H_{arom}), 8.23–8.58 (m, 2H_{arom})
2g	15	91	189–190	$C_{15}H_9ClN_2O_6$ (348.7)	1714	6.38 (s, 1H, H-2), 7.07–7.40 (m, 2H, H-6, 7), 7.53–7.85 (m, 1H, H-8), 7.67 and 8.27 (AA′BB′ system, 4H_{arom}, $C_6H_4NO_2$), 8.07 (dd, 1H, $J_{5,7} = 1.8$, $J_{5,6} = 7.8$, H-5)
2h	8	90	122–123	$C_{16}H_{12}ClNO_5$ (333.7)	1709	3.72 (s, 3H, OCH_3), 6.70 (s, 1H, H-2), 6.77–7.90 (m, 7H_{arom}), 7.97–8.15 (m, 1H, H-5)
2i	8	83	86–88	$C_{16}H_{12}ClNO_5$ (333.7)	1713	3.82 (s, 3H, OCH_3), 6.25 (s, 1H, H-2), 6.85–7.48 (m, 6H_{arom}), 7.55–7.80 (m, 1H_{arom}), 7.95–8.15 (m, 1H, H-5)
2j	8	90	123–124	$C_{16}H_{12}ClNO_5$ (333.7)	1713	3.80 (s, 3H, OCH_3), 6.18 (s, 1H, H-2), 6.89 and 7.40 (AA′BB′ system, 4H_{arom}, $C_6H_4OCH_3$), 7.03–7.50 (m, 2H_{arom}), 7.51–7.78 (m, 1H_{arom}), 7.92–8.17 (m, 1H, H-5)
2k	15	85	120–121	$C_{18}H_{16}ClNO_7$ (393.8)	1713	3.87 (s, 9H, 3 × OCH_3), 6.18 (s, 1H, H-2), 6.68 (s, 2H, H-2′, 6′), 7.08–7.37 (m, 2H_{arom}), 7.53–7.82 (m, 1H_{arom}), 7.97–8.17 (m, 1H_{arom})
2l	48	88	188–189	$C_{16}H_{11}Cl_2NO_5$ (368.2)	1707	3.93 (s, 3H, OCH_3), 6.20 (s, 1H, H-2), 6.65 and 6.71 (2dd, 2H, $J_{6,7} = J_{7,8} = 8.4$, H-6 and H-8), 7.40 (br s, 4H_{arom}, C_6H_4Cl), 7.57 (t, 1H, $J_{6,7} = J_{7,8} = 8.4$, H-7)
2m	15	96	179–180	$C_{16}H_{11}Cl_2NO_5$ (368.2)	1708	3.83 (s, 3H, OCH_3), 6.18 (s, 1H, H-2), 7.08 (dd, 1H, $J_{5,7} = 1.2$, $J_{7,8} = 9.0$, H-7), 7.30 (d, 1H, $J_{7,8} = 9.0$, H-8), 7.40 (s, 4H_{arom}, C_6H_4Cl), 7.40 (m, 1H, H-5)
2n	8	91	147–148	$C_{16}H_{11}Cl_2NO_5$ (368.2)	1703	3.88 (s, 3H, OCH_3), 6.22 (s, 1H, H-2), 6.57 (d, 1H, $J_{6,8} = 2.4$, H-8), 6.75 (dd, 1H, $J_{6,8} = 2.4$, $J_{5,6} = 9.0$, H-6), 7.38 (s, 4H_{arom}, C_6H_4Cl), 7.93 (d, 1H, $J_{5,6} = 9.0$, H-5)
2o	15	93	182–183	$C_{16}H_{11}Cl_2NO_5$ (368.2)	1715	3.88 (s, 3H, OCH_3), 6.23 (s, 1H, H-2), 7.12–7.35 (m, 2H_{arom}), 7.42 (s, 4H_{arom}, C_6H_4Cl), 7.55–7.73 (m, 1H_{arom})
2p	24	88	210–212	$C_{15}H_7Br_2Cl_2NO_4$ (495.9)	1721	6.28 (s, 1H, H-2), 7.43 (s, 4H_{arom}, C_6H_4Cl), 7.93–8.18 (m, 2H, H-5, 7),
2q	15	93	183–184	$C_{15}H_8Cl_3NO_4$ (372.6)	1718	6.22 (s, 1H, H-2), 7.13 (d, 1H, $J_{7,8} = 8.7$, H-8), 7.43 (s, 4H_{arom}, C_6H_4Cl), 7.63 (dd, 1H, $J_{5,7} = 2.4$, $J_{7,8} = 8.7$, H-7), 8.00 (d, 1H, $J_{5,7} = 2.4$, H-5)
2r	24	73	163–165	$C_{15}H_8Cl_2N_2O_6$ (383.1)	1727	6.37 (s, 1H, H-2), 7.37 (d, 1H, $J_{7,8} = 9.3$, H-8), 7.47 (s, 4H_{arom}, C_6H_4Cl), 8.53 (dd, 1H, $J_{5,7} = 2.7$, $J_{7,8} = 9.3$, H-7), 8.97 (d, 1H, $J_{5,7} = 2.7$, H-5)

[a] Yield of pure recrystallized product based on **1**.

[b] The following solvents were used for recrystallization: heptane (**2a,b, g–j, m, n, q**), hexane (**2c, d, k**), cyclohexane/benzene (**2e, l**), hexane/benzene (**2f**) and heptane/benzene (**2o, p, r**).

[c] Satisfactory microanalyses obtained: C ±0.30, H ±0.13, N ±0.17.

range of starting materials **1** bearing either electron-donating groups or/and electron-withdrawing substituents in various positions, proved to be quite general. Three 3-nitroflavones have already been prepared by Rao and co-workers, in moderate cumulative yields, following a three-step procedure starting from 2′-hydroxy-2-nitroacetophenones and aryl aldehydes.[3] The 3-nitroflavone (**3a**) itself has also been obtained by Michalska, in about 42 % overall yield, according to a multistep process starting from flavanone.[4,5] However, the scopes of these previously reported routes remain considerably restricted, because conveniently substituted starting materials are not readily available. Furthermore, undesirable side reactions, such as electrophilic brominations, can occur.[3] On the other hand, it is worth recalling that the acidic treatment of 2′-benzyloxy-α-nitrochalcone epoxides has been reported to give, probably through the 3-hydroxy-3-nitroflavanone derivatives, 3-hydroxyflavones and not the 3-nitroflavones whose formation could have been expected from the same intermediates under such conditions.[6,7]

Melting points were measured using an Electrothermal melting point apparatus and are uncorrected. ^1H NMR spectra were determined at 90 MHz with a Varian EM 390 spectrometer. IR spectra were recorded on a Perkin-Elmer 1710 spectrophotometer in $CHCl_3$. Microanalyses were performed by the "Service d'Analyse du

Table 2. 2-Aryl-3-nitro-2-phenyl-4*H*-1-benzopyran-4-ones **3** Prepared

Product	Reaction Time (min)	Yield[a] (%)	mp (°C)[b]	Molecular Formula[c] or Lit. mp (°C)	IR ($CHCl_3$) $\nu_{C=O}$ (cm^{-1})	^1H NMR ($CDCl_3$/TMS) δ, *J* (Hz)
3a	20	92	140–141	139[3] 140.5–141.5[5]	1666	7.33–7.93 (m, 8 H_{arom}), 8.20–8.40 (m, 1 H, H-5)
3b	20	82	119–121	$C_{15}H_8ClNO_4$ (301.7)	1673	7.38–8.00 (m, 7 H_{arom}), 8.30–8.53 (m, 1 H, H-5)
3c	20	95	157–158	$C_{15}H_8ClNO_4$ (301.7)	1671	7.28–7.93 (m, 7 H_{arom}), 8.18–8.55 (m, 1 H, H-5)
3d	20	90	161–162	$C_{15}H_8ClNO_4$ (301.7)	1667	7.48 and 7.67 (AA'BB' system, 4 H_{arom}, C_6H_4Cl), 7.35–7.92 (m, 3 H, H-6, 7, 8), 8.18–8.40 (m, 1 H, H-5)
3e	20	72	209–210	$C_{15}H_8N_2O_6$ (312.2)	1674	7.35–7.92 (m, 6 H_{arom}), 8.25–8.48 (m, 2 H, H-5, 3'),
3f	20	76	199–200	$C_{15}H_8N_2O_6$ (312.2)	1672	7.42–8.15 (m, 5 H_{arom}), 8.25–8.57 (m, 2 H_{arom}), 8.62–8.73 (m, 1 H_{arom})
3g	20	74	183–185	$C_{15}H_8N_2O_6$ (312.2)	1672	7.42–7.68 (m, 2 H_{arom}), 7.69–8.02 (m, 1 H_{arom}), 7.90 and 8.37 (AA'BB' system, 4 H_{arom}, $C_6H_4NO_2$), 8.25–8.48 (m, 1 H_{arom})
3h	60	89	169–171	$C_{16}H_{11}NO_5$ (297.3)	1662	3.82 (s, 3 H, OCH_3), 6.85–7.28 (m, 2 H_{arom}, 7.32–7.88 (m, 5 H_{arom}), 8.22–8.42 (m, 1 H, H-5)
3i	20	93	141–143	$C_{16}H_{11}NO_5$ (297.3)	1662	3.83 (s, 3 H, OCH_3), 7.02–7.92 (m, 7 H_{arom}), 8.18–8.38 (m, 1 H, H-5)
3j	120	95	146–147	$C_{16}H_{11}NO_5$ (297.3)	1657	3.88 (s, 3 H, OCH_3), 6.99 and 7.70 (AA'BB' system, 4 H_{arom}, $C_6H_4OCH_3$), 7.32–7.88 (m, 3 H_{arom}), 8.17–8.37 (m, 1 H, H-5)
3k	20	91	177–178	$C_{18}H_{15}NO_7$ (357.3)	1662	3.87 (s, 6 H, 2 × OCH_3), 3.92 (s, 3 H, OCH_3), 6.93 (s, 2 H_{arom}), 7.35–7.92 (m, 3 H, H-6, 7, 8), 8.30 (dd, 1 H, $J_{5,7} = 1.8$, $J_{5,6} = 7.8$, H-5)
3l	20	90	233–235	$C_{16}H_{10}ClNO_5$ (331.7)	1661	4.00 (s, 3 H, OCH_3), 6.88 (br d, 1 H, $J_{6,7} = 8.4$, H-6), 7.08 (dd, 1 H, $J_{6,8} = 1.2$, $J_{7,8} = 8.4$, H-8), 7.48 and 7.66 (AA'BB' system, 4 H_{arom}, C_6H_4Cl), 7.65 (t, 1 H, $J_{6,7} = J_{7,8} = 8.4$, H-7)
3m	20	93	189–190	$C_{16}H_{10}ClNO_5$ (331.7)	1661	3.90 (s, 3 H, OCH_3), 7.25–7.75 (m, 3 H_{arom}, H-5, 7, 8), 7.48 and 7.65 (AA'BB' system, 4 H_{arom}, C_6H_4Cl)
3n	20	87	183–185	$C_{16}H_{10}ClNO_5$ (331.7)	1661	3.93 (s, 3 H, OCH_3), 6.88–7.18 (m, 2 H, H-6, 8), 7.47 and 7.65 (AA'BB' system, 4 H_{arom}, C_6H_4Cl), 8.17 (br d, 1 H, $J_{5,6} = 8.4$, H-5)
3o	20	89	186–187	$C_{16}H_{10}ClNO_5$ (331.7)	1665	3.98 (s, 3 H, OCH_3), 7.12–7.88 (m, 3 H, H-5, 6, 7), 7.47 and 7.70 (AA'BB' system, 4 H_{arom}, C_6H_4Cl)
3p	20	78	229–230	$C_{15}H_6Br_2ClNO_4$ (459.5)	1671	7.53 and 7.75 (AA'BB' system, 4 H_{arom}, C_6H_4Cl), 8.12 (br d, 1 H, $J_{5,7} = 2.4$, H-7), 8.38 (br d, 1 H, $J_{5,7} = 2.4$, H-5)
3q	20	85	201–202	$C_{15}H_7Cl_2NO_4$ (336.1)	1670	7.38–7.85 (m, 2 H, H-7, 8), 7.51 and 7.67 (AA'BB' system, 4 H_{arom}, C_6H_4Cl), 8.25 (br d, 1 H, $J_{5,7} = 2.4$, H-5)
3r	20	86	196–197	$C_{15}H_7ClN_2O_6$ (346.7)	1679	7.51 and 7.69 (AA'BB' system, 4 H_{arom}, C_6H_4Cl), 7.75 (d, 1 H, $J_{7,8} = 9.0$, H-8), 8.62 (dd, 1 H, $J_{5,7} = 3.0$, $J_{7,8} = 9.0$, H-7), 9.13 (br d, 1 H, $J_{5,7} = 3.0$, H-5)

[a] Yield of pure recrystallized product based on **2**.

[b] Compounds **3a, c, f – r** were recrystallized from heptane/benzene, **3b** from hexane/benzene, **3d** from cyclohexane/benzene and **3e** from EtOAc/benzene.

[c] Satisfactory microanalyses obtained: C ±0.29, H ±0.14, N ±0.18

CNRS", Vernaison. TLC was carried out with Merck silica gel $60F_{254}$, TLC plates (200 μ). A Bransonic 220 apparatus (50 kHz) was used as the ultrasonic generator. Starting 2-aryl-3-chloro-3,4-dihydro-4-hydroxy-3-nitro-2*H*-1-benzopyrans **1a–r** were prepared according to a previously described procedure.[2] PCC and DBU were purchased from Janssen Chimica and were used without further purification. CH_2Cl_2 and THF were dried prior to use by distillation from phosphorous pentoxide or from benzophenone/sodium, respectively.

2-Aryl-3-chloro-2,3-dihydro-3-nitro-4*H*-1-benzopyran-4-ones 2a–r; General Procedure:

To a solution of appropriate benzopyran **1a–r** (10 mmol) in anhydrous CH_2Cl_2 (50 mL), in a dried, two-necked, 100-mL round-bottomed flask fitted with a condenser surmounted by a drying tube, was added PCC (4.31 g, 20 mmol). The flask, whose joints were efficiently maintained tight with clips, was immersed in an ultrasound bath. The temperature of the bath increased gradually from r.t. to about 55 °C during the course of the reaction, and the progress of the oxidation was followed by TLC (eluent: CH_2Cl_2). After the reported time (Table 1), the reaction mixture was filtered by suction, and the separated solid was thoroughly rinsed with several portions of CH_2Cl_2. The combined CH_2Cl_2 solutions were evaporated under reduced pressure to leave a residue which was chromatographed on a silica gel column (50 g, 230–400 mesh ASTM, eluent: CH_2Cl_2). Removal of the solvent, followed by recrystallization, gave analytically pure compounds **2a–r** in the reported yields (Table 1).

In the case of **2l**, the reaction was much slower (probably because of the steric hindrance due to the presence of a methoxy group in the 5-position), and a slightly larger excess of PCC (5.39 g, 25 mmol) had been employed.

2-Aryl-3-nitro-4*H*-1-benzopyrans 3a–r; General Procedure:

A solution of the appropriate benzopyranone **2a–r** (5 mmol) in anhydrous THF (25 mL) was prepared in a flame-dried, two-necked, 100-mL round-bottomed flask fitted with a septum inlet. The mixture was stirred with a magnetic bar under Ar atmosphere, then DBU (0.837 g, 0.823 mL, 5 mmol) was added in one portion with a syringe. The reaction was moderately exothermic whilst a modification of the colour occured. The progress of the reaction was monitored by TLC (eluent: CH_2Cl_2). When the starting material had completely disappeared (Table 2), CH_2Cl_2 (50 mL) and 0.1 N HCl (15 mL) were successively added to the reaction mixture. The organic phase was separated and the aqueous layer was extracted with CH_2Cl_2 (3 × 10 mL). The combined organic extracts were dried ($MgSO_4$), filtered, and evaporated in vacuo to provide a crude product which was flash-chromatographed over a silica gel column (30 g, 230–400 mesh ASTM, eluent: CH_2Cl_2). Evaporation of CH_2Cl_2, followed by recrystallization from a suitable solvent afforded pure products **3a–r** (Table 2).

---

(1) The literature survey reveals an abundance of general publications relevant to flavones and flavonoids. See for example:
Geissman, T. A. *The Chemistry of Flavonoid Compounds*, Pergamon Press: Oxford, 1962.
Dean, F. M. *Naturally Occuring Oxygen Ring Compounds*, Butterworths: London, 1963.
Lutomski, J.; Szpunar, K. *Deut. Apoth. Ztg.* **1972**, *112*, 553.
The Flavonoids, Harborne, J. B.; Mabry, T. J.; Mabry, H. Eds., Chapman & Hall: London, 1975.
Morita, N.; Arisawa, M. *Heterocycles* **1976**, *4*, 373.
Swain, T. In *Chemistry and Biochemistry of Plants Pigments*, 2nd ed., Goodwin, T. W. Ed., Academic: London, 1976, p 425.
Staunton, J. In: Barton and Ollis, *Comprehensive Organic Chemistry*, Vol. 4. Sammes, P. G. Ed., Pergamon Press: Oxford, 1979, p. 681.
The Flavonoids: Advances in Research, Harborne, J. B.; Mabry, T. J. Eds.; Chapman & Hall: London, 1982.
Havsteen, B. *Biochem. Pharmacol.* **1983**, *32*, 1141.
Progress in Clinical and Biological Research, Vol. 213 *Plant Flavonoids in Biology and Medicine*, Cody, V.; Middleton, E.; Harborne, J. B. Eds., Alan R. Liss. Inc.: New York, 1986.
The Flavonoids: Advances in Research since 1980, Harborne, J. B. Ed., Chapman & Hall: New York, 1988.
Progress in Clinical and Biological Research, Vol. 280, *Plant Flavonoids in Biology and Medicine II*, Cody, V.; Middleton, E.; Harborne, J. B.; Beretz, A. Eds., Alan, R. Liss. Inc.: New York, 1988.
Iinuma, M.; Mizuno, M. *Phytochemistry* **1989**, *28*, 681.
Bertram, B. *Dtsch. Apoth. Ztg.* **1989**, *129*, 2561.

(2) Dauzonne, D.; Demerseman, P. *Synthesis* **1990**, 66.

(3) Paparao, C.; Rao, K. V.; Sundaramurthy, V. *Synthesis* **1981**, 236.

(4) Michalska, M. *Chem. Ind. (London)* **1966**, 628.

(5) Michalska, M. *Bull. Acad. Pol. Sci., Ser. Sci. Chem.* **1968**, *16*, 567.

(6) Shakhova, M. K.; Litkei, Yu; Samokhvalov, G. I. *Dokl. Akad. Nauk. SSSR.* **1963**, *151*, 1120; *Dokl. Chem. (Engl. Transl.)* **1963**, *151*, 644.

(7) Budagyants, M. I.; Shakhova, M. K.; Samokhvalov, G. I. *Zhur. Org. Khim.* **1969**, *5*, 1857; *J. Org. Chem. USSR (Engl. Transl.)* **1969**, *5*, 1803.